Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for secukinumab

Proprietary Product Name: Cosentyx / Zafrez

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

First round CER: September 2015

Second round CER: January 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
AE	Adverse Event
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
CRP	C-Reactive Protein
CS	Corticosteroids
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-Rheumatic Drug
EE	Early Escape
ES	Erosion Score
ESR	Erythrocyte Sedimentation Ratio
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
IL	Interleukin

Abbreviation	Meaning
IR	Inadequate Responder
IV	Intravenous
JSN	Joint Space Narrowing
LLOQ	Lower Limit of Quantification
LS	Least Square
MACE	Major Adverse Cardiovascular Event
MCR	Major Clinical Response
MTX	Methotrexate
NRI	Non-Responder Imputation
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area Severity Index
PBO	Placebo
PD	Pharmacodynamic
PhGA	Physician Global Assessment (of disease activity)
PK	Pharmacokinetic
PsA	Psoriatic Arthritis
PtGA	Patient Global Assessment (of disease activity)
PY	Patient-Years
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SEK	Secukinumab
SOC	System Organ Class
TB	Tuberculosis
TNF	Tumour Necrosis Factor

Abbreviation	Meaning
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
vdH-mTSS	van der Heijde - modified Total Sharp Score

1. Introduction

This report will evaluate 2 complete submissions to extend the treatment indications for secukinumab (SEK) to include active psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The sponsor application letters for each application are dated 4th and 1st May 2015, respectively. SEK is currently registered in Australia for use in adult patients with plaque psoriasis (PSOR). It was approved for this indication in January 2015 (Submission ID: PM-2013-04153-1-4).

For the requested indication of PsA, the submission contains 2 pivotal Phase 3 trials (Studies F2306 and F2312), which are of similar design; as well as 1 supporting Phase 2 trial (Study A2206) of 24 weeks duration followed by an open-label extension phase (Study A2206E1) with up to 52 weeks of additional therapy. Both of the pivotal Phase 3 PsA trials provided efficacy and safety information for up to 52 weeks of treatment.[1] Interim study reports for both studies were provided in this submission. Just over 1000 subjects in total were recruited into the Phase 3 PsA trials. Both of the pivotal studies are ongoing with a total planned duration of 2-5 years. For the PsA indication, the sponsor has also included data from the subset of patients with PsA as a co-morbidity who were involved in the pivotal PSOR studies. All of the supporting PsA studies are complete and the final study reports have been included in this submission.

In support of the extension of treatment indication for SEK to include AS, this submission contains 2 pivotal Phase 3 studies (F2305 and F2310) of similar design, as well as 1 supportive Phase 2 trial (A2209) of 28 weeks duration, which enrolled a total of 60 patients. The Phase 2 trial also had an open-label extension period (A2209E1) of up to 52 weeks duration, which enrolled a total of 39 patients. Both of the Phase 3 studies are ongoing with interim study reports up to 52 weeks of treatment follow-up being included in this submission. A total of 590 patients were enrolled in the 2 Phase 3 studies, of which 394 subjects received SEK (either 75 mg or 150 mg injections) in the first 16 weeks (i.e. the true PBO-controlled period). In total, >90% of subjects completed their week 16 assessment (primary endpoint) and ~85% of patients completed 52 weeks of treatment follow-up in the Phase 3 AS program.

SEK is currently approved for the treatment of moderate to severe PSOR in adult patients under the registered trade name of "Cosentyx". The sponsor does not propose a different registered drug name for this indication. No change in the drug formulation or presentation is proposed.

2. Clinical rationale

2.1. Psoriatic arthritis

PsA is a chronic inflammatory arthritis associated with skin psoriasis which typically onsets between the ages of 30 and 55 years, and affects men and women equally. Skin psoriasis has a prevalence in the general population of 2-3%, and it is estimated that approximately 30% of patients with PSOR develop PsA (Mease 2011).

PsA is a multifaceted and heterogeneous disease, which affects the joints, soft tissues (enthesitis and dactylitis) and skin. All of the disease manifestations may affect functional capacity and QOL. There is also increased mortality with persistent, severely active PsA. Peripheral joint involvement with PsA may be polyarticular (35-40%) or oligoarticular (20-35%), and axial involvement (spondylitis) has been reported in 10-25% of patients. The PsA radiographic spectrum is highly variable and includes patients with mild, non-destructive disease to those

[1] The submission package contained the Week 52 CSR for Study F2306, but only the Week 24 CSR for Study F2312.

with severe and debilitating deformities due to progressive joint disease. The diverse radiographic findings seen in PsA include erosions and joint space narrowing (JSN), soft tissue changes, and new bone formation.

SEK neutralises the bioactivity of IL-17A, which is a key pro-inflammatory cytokine predominantly secreted by a subset of T-helper cells, known as Th-17 cells. IL-17A is highly expressed in the synovium and entheses of patients with PsA, and patients with PSOR over-express this key pro-inflammatory cytokine in psoriatic plaques. In addition, mouse models of arthritis demonstrate that the injection of IL-17A has the capacity to provoke and maintain entheseal inflammation. By selectively binding IL-17A, SEK appears to have robust biological plausibility in being able to treat both psoriasis and PsA (Kirkham et al, 2014; McInnes et al, 2014 and Gottlieb et al, 2014).

Current approved treatment options in Australia for moderately to severely active PsA include NSAIDs; conventional non-biological DMARDs such as methotrexate (MTX), sulfasalazine, leflunomide and cyclosporine; apremilast; anti-TNF drugs and ustekinumab. Recent literature suggests that conventional DMARDs have modest efficacy in treating the signs and symptoms of PsA. In addition, while anti-TNF drugs have been shown to demonstrate significant efficacy in treating active PsA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for anti-TNF therapies, ACR20 response rates range from 50-60% and ACR50 response rates are approximately 30-40%. As such, there is an unmet need for additional therapies for active, treatment refractory PsA. SEK is a monoclonal antibody therapy that has a different mechanism of action to conventional DMARDs, apremilast and anti-TNF drugs.

2.2. Ankylosing spondylitis

AS is a chronic inflammatory arthritis, which primarily affects the axial skeleton, but peripheral joints and extra-articular structures may also be involved. It has a prevalence of approximately 1 in 200 adults and the majority (85-90%) of affected individuals carry the HLA-B27 gene. The main clinical symptom of AS is inflammatory back pain, typically starting in the sacroiliac joints (buttock area) and lumbar spine. However, patients may develop musculoskeletal symptoms away from the spine (peripheral joint arthritis and enthesitis), as well as extra-articular manifestations (colitis, uveitis, skin psoriasis). Between 30-60% of AS patients have significant functional loss within 2 years of diagnosis. Early in the disease, disability is determined mainly by inflammatory activity, whereas in long-standing established disease, both inflammation and bony ankylosis contribute to disability.

The modified New York criteria for the diagnosis of AS were developed nearly 30 years ago, and have been widely accepted in clinical practice and trials (van der Linden et al, 1984). The modified New York diagnostic criteria work well in established disease, but have limited utility in detecting early disease. The criteria require clear evidence of sacroiliitis on conventional plain X-rays, but MRI has the ability to reliably detect and follow the radiographic progression of AS over shorter time frames (several months versus 1-2 years with plain X-rays).

The pathogenesis of AS is complex, but one of the key processes involved is the development and differentiation of Th-17 cells, mainly as a result of excess production of IL-23. By selectively targeting the predominant cytokine produced by helper Th-17 cells, IL-17A inhibition with SEK represents a potentially novel approach to interfere with the chronic inflammatory process associated with AS. IL-17A is highly expressed in the spinal facet joints and peripheral joint synovium of patients with AS. Furthermore, in animal models of AS, IL-17A has a direct link to facilitating the structural damage in the axial skeleton by reducing receptor activation of nuclear factor kappa-B ligand (RANKL) dependent osteoclastogenesis. By selectively binding IL-17A, SEK appears to have robust biological plausibility in being able to treat AS, both from a symptomatic and structural viewpoint.

The main treatment options available for AS are NSAIDs and physiotherapy. Non-biologic DMARDs such as MTX and sulfasalazine, as well as CS may be tried, but the supporting evidence of efficacy is very limited to non-existent. Five anti-TNF drugs (infliximab, etanercept, adalimumab, certolizumab and golimumab) are currently registered in Australia, Europe and the USA for the treatment of AS in terms of improving the signs and symptoms of spinal and peripheral arthritis, physical functioning and health related quality of life. In addition, while anti-TNF drugs have been shown to demonstrate significant efficacy in treating active AS, a significant proportion of patients are not achieving meaningful ASAS (Assessment of Spondyloarthritis International Society) responses. Based on the current literature for anti-TNF therapies, ASAS20 response rates range from 47-61% and ASAS40 response rates range from 40-47%. There is an unmet need for additional therapies for active, treatment refractory AS and SEK is a monoclonal antibody therapy that has a different mechanism of action to NSAIDs, conventional DMARDs and anti-TNF drugs.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

3.1.1. Psoriatic Arthritis

- No specific clinical pharmacology studies were conducted, but pharmacokinetic (PK) data was collected in the 2 pivotal, efficacy/safety Phase III studies (F2306 and F2312) and the dose finding, proof-of-concept Phase II trial (A2206).
- 1 population PK analysis of pooled data obtained in Studies F2306, F2312 and A2206.
- Meta analysis report of total IL-17A (the same as provided in the AS application).
- 2 pivotal, Phase III efficacy/safety studies (F2306 and F2312).
- 1 supporting Phase II, proof-of-concept study (A2206) and its open-label extension phase (A2206E1).
- Safety data from an additional 35 trials, in which SEK was investigated for the treatment of various other autoimmune conditions (such as PSOR, RA, Crohn's disease, uveitis, multiple sclerosis, dry eye syndrome and polymyalgia rheumatic).
- Integrated efficacy data analysis by pooling the data from the Phase III and 3 PsA studies.

3.1.2. Ankylosing Spondylitis

- No specific clinical pharmacology studies were conducted, but PK data was collected in the 2 pivotal, efficacy/safety Phase III studies (F2305 and F2310) and the dose finding, proof-of-concept Phase II trial (A2209).
- 1 population PK analysis of pooled data obtained in Studies F2305, F2310 and A2209.
- Meta-analysis Report of Total IL-17A (the same as provided in the PsA application).
- 2 pivotal, Phase III efficacy/safety studies (F2305 and F2310).
- 1 supporting, Phase II, dose finding study (A2209) and its open label extension phase (A2209E1).
- Safety data from an additional 35 trials, in which SEK was investigated for the treatment of various other autoimmune conditions (such as PSOR, RA, Crohn's disease, uveitis, multiple

sclerosis, dry eye syndrome and polymyalgia rheumatic) – as per the expanded safety dataset provided in the PsA application.

- Integrated efficacy data analysis by pooling the data from the Phase III and 3 AS studies.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All of the studies in the SEK clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements were met.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

In both treatment indications, PK data was collected in the pivotal Phase 3 studies (n=2 for each treatment indication) as well as the supporting Phase 2 trial (n=1 for each indication). The PK data collected in each treatment indication was then used to develop a population PK model for each treatment indication. The population PK model already developed in adult patients with PSOR was used to provide some of the baseline assumptions in each of the new population PK models. None of the PK studies in either treatment indication had deficiencies that excluded their results from consideration. In the Phase 3 studies in both indications, 2 SEK treatment regimens were investigated. Firstly, SEK was given by SC injection in doses of 75 mg, 150 mg or 300 mg (highest dose only in PsA subjects) using a loading regimen (weekly for the first 4 weeks) followed by a maintenance regimen of every 4 weeks starting at week 4 (Study F2312 in PsA and Study F2310 in AS). The second SEK regimen investigated in the Phase 3 studies (Study F2306 in PsA and Study F2305 in AS) involved 3 x 10 mg/kg IV loading doses over a 4 weeks period (weeks 0, 2 and 4) followed by a fixed interval dosing with SC SEK 75 mg or 150 mg injections every 4 weeks starting at week 4.

Table 1 provides a summary of the PsA clinical studies that collected PK data, which was used in the population PK analysis of SEK use in adult patients with active PsA. In addition to the 2 Phase 3 studies in PsA, there was a single, Phase 2, proof-of-concept trial (A2206), which investigated the efficacy, safety and PK characteristics of 2 x 10 mg/kg SEK doses given 3 weeks apart.

Table 1: Summary of Clinical Studies providing Pharmacokinetic Data in Psoriatic Arthritis.

Study	Description	Regimens	Note
A2206	PoC PD study of efficacy of AIN457	• 2 x 10 mg/kg i.v. q3w • placebo	PK samples taken pre-dose, 2, 3, 4 and 24 hours after infusion, and then at weeks 1, 2, 3, 4, 6, 8 ,10, 12, 16, 20 and 24/end of study
F2306*	Phase III efficacy safety and tolerability	• 3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from week 8 • 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8 • placebo + 150 mg s.c. q4w from week 24 • placebo + 75 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo	PK samples at weeks 0, 4, 16, 24, 52
F2312**	Phase III efficacy, safety and tolerability	• 4 x 300 mg s.c. q1w + 300 mg s.c. q4w from week 4 • 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75mg s.c. q4w from week 4 • placebo + 300 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 24 • placebo + 300 mg s.c. q4w from week 16 • placebo + 150 mg s.c. q4w from week 16 • placebo	PK samples at weeks 0, 4, 16, 24

* F2306: Week 52 interim lock
** F2312: Week 24 interim lock

Table 2 provides a summary of the AS clinical studies that collected PK data, which was used in the population PK analysis of SEK use in adult patients with active AS. In addition to the 2 Phase 3 studies in AS, there was a single, Phase 2, proof-of-concept trial (A2209), which investigated the efficacy, safety and PK characteristics of 3 different doses of SEK (0.1 mg/kg, 1.0 mg/kg and 10 mg/kg) given on 2 occasions by IV infusion, 3 weeks apart.

Table 2: Summary of Clinical Studies providing Pharmacokinetic Data in Ankylosing Spondylitis.

Study	Description	Regimens	Note
A2209	PoC PD study of efficacy of AIN457	• 2 x 0.1 mg/kg i.v. q3w • 2 x 1 mg/kg i.v. q3w • 2 x 10 mg/kg i.v. q3w • placebo	PK samples taken pre-dose, 2, 3, 4 and 24 hours after infusion, and then at weeks 1, 2, 3, 4, 6, 8 , 12, 16, 20, 24 and 28/end of study
F2305*	Phase III efficacy safety and tolerability	• 3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from week 8 • 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8 • placebo + 150 mg s.c. q4w from week 24 • placebo + 75 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo	PK pre-dose samples in weeks 0, 4, 16, 24 and 52. For premature discontinuation, samples at 4 weeks after last dose.
F2310**	Phase III efficacy, safety and tolerability	• 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo	PK pre-dose samples in weeks 0, 4, 16

* F2305: Week 52 interim lock
** F2310: Week 16 interim lock

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans with supporting information derived from the sponsor's summaries, as well as the currently approved product information (PI).

4.2.1. Physicochemical characteristics of the active substance

SEK is a humanised monoclonal antibody of the IgG1/kappa isotype, comprised of heavy (containing 457 amino acids) and light chain segments (containing 215 amino acids). It binds with high affinity to the pro-inflammatory cytokine IL-17A and blocks its interaction with the IL-17 receptor, which is expressed on a variety of cell types within the body. SEK has an approximate molecular weight of 148 kDa. It is produced by recombinant technology in Chinese Hamster Ovary cells. The sponsor does not propose any change to the physiochemical structure or manufacturing process of SEK with these applications for extension of treatment indication.

4.2.2. Pharmacokinetics in healthy subjects

The PK characteristics of SEK administered by SC injection in healthy volunteers and adult patients with moderate to severe PSOR have already been evaluated in the original registration submission in Australia. The current submissions did not contain any additional PK information acquired in healthy volunteers.

A summary of the key PK findings from that original submission is provided. SEK is slowly absorbed from the site of SC injection, reaching maximum serum concentration 5-6 days after administration. Absolute bioavailability in healthy Japanese males is 77% (73% in adult subjects with PSOR), which is similar to the bioavailability for human IgG (65 – 67%). No studies have examined the effects of food or administration timing on the PK of SEK.

In healthy volunteers following a single SC dose of 300 mg SEK (via prefilled syringe), the mean C_{max} and AUC_{inf} were 43.2 µg/mL and 1785 µg/mL respectively. The median T_{max} occurred 5 hours after dosing and the mean $t_{1/2}$ is 26.6 hours. Dose proportionality has not been demonstrated for C_{max} and AUC following SC injection of 150 mg and 300 mg of SEK in healthy Japanese males. Following SC injection of 150 mg SEK, the inter-subject variability (CV%) in C_{max} and AUC_{inf} for healthy volunteers ranged from 13.8-27.7% and 14.3-26.7%, respectively. In patients with PSOR, C_{max} and AUC was dose proportional for the 150 mg and 300 mg SC doses.

The mean apparent volume of distribution following 150 mg of SC administered SEK in adults is 6.6 L. The mean volume of distribution following single IV administration ranges from 7.1-8.6 L in adult subjects with PSOR. Overall, the volume of distribution data suggests that SEK undergoes limited distribution to peripheral compartments.

The mean elimination half-life of SEK is estimated to be 27 days (range: 18-46 days) in adult patients with PSOR. Although no studies have examined the metabolic pathways involved in SEK metabolism, it is expected that the drug be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. No specific studies have been performed to assess the effect of renal or hepatic impairment on the PK of SEK. Age and gender do not appear to be significant factors in determining the PK characteristics of SEK in adult patients with PSOR.

The key PK variables observed in adult patients with PSOR are similar and consistent in general with those seen in healthy subjects.

4.2.3. Pharmacokinetics in the target population

Before assessing the PK data, the following outlines 2 key issues regarding methodology:

4.2.3.1. Method of analysing serum SEK concentrations

Total SEK concentrations (i.e. free SEK plus SEK bound to IL-17A) were analysed in human serum using a specific validated ELISA method, which had a lower limit of quantification (LLOQ) of 80 ng/mL (=0.08 µg/mL). The intra-day accuracy and intra-day precision were within the range of 76.4% to 118% and within the range of 1.4% to 17.8%, respectively. The inter-day accuracy and inter-day precision were within the range of 89.6% to 99.0% and 7.2% to 15.6%, respectively. Serum stored for estimation of SEK concentrations was proven to be stable at -20°C for at least 20 months. In the Phase 3 studies for both treatment indications, venous blood samples for PK analysis were to be collected pre-dose at baseline, and weeks 4, 16, 24 and 52.

4.2.3.2. Background to population PK models

A previous population PK model of SEK in adult patients with moderately severe PSOR demonstrated that the PK of SEK is well described using a linear 2-compartment model, with first-order absorption for SC administration and a constant rate infusion for IV administration. The model in PSOR was used as the starting point for the planned population PK analyses in both the PsA and AS cohorts. The descriptive and predictive capabilities of each population PK model were appropriately validated using goodness-of-fit plots and predictive checks.

In each treatment indication, several covariates were investigated for a potential impact on the PK of SEK. These covariates included subject body weight, age, gender, race (Asian versus non-Asian), time since diagnosis, prior anti-TNF status (naïve or experienced), number of previously used anti-TNF drugs (1 versus 2 or more), concomitant use of MTX and disease activity at baseline (relevant clinical index and CRP). For the categorical covariate factors like prior anti-TNF status, the covariate describes naïve versus inadequate responder status. For continuous covariate factors, the high and low covariate factors (i.e. the 95% and 5% percentiles of the covariate distribution) were used. For subject weight in PsA patients, the reference (or typical patient) weighed 84 kg, so the range of 55 kg to 120 kg was assessed. For baseline CRP values in the AS cohort, the reference reading was 5.5 mg/L, with the range being 0.7 mg/L to 48.6 mg/L. For subject weight in AS patients, the reference (or typical patient) weighed 77 kg, so the range

of 53 kg to 112 kg was assessed. For baseline CRP values in the AS cohort, the reference reading was 7.38 mg/L, with the range being 0.7 mg/L to 64 mg/L. In both treatment indications, it was assumed that change to the typical subject parameter of >20% was of potential clinical significance.

4.2.3.3. Psoriatic arthritis

For the PK analysis in PsA, a total of 755 subjects contributed data (28 subjects in Study A2206, 472 patients in Study F2305 and 255 subjects in Study F2312). Table 3 lists all the treatment groups included in the PK analysis for PsA, as well as their received treatment and PK observations. A total of 344 records (affecting 251 subjects) were excluded from the PK analysis, mainly because blood collections were taken outside of the scheduled visit time window (302 records affecting 219 subjects). In addition, a total of 982 PK observation records had serum concentrations of SEK below the LLOQ. This included 974 samples collected before any active study treatment was commenced and 8 of these records occurred after drug dosing had occurred.

Table 3: Summary of Treatment Groups and the PK Analysis Set for Psoriatic Arthritis.

Group	N	records	active doses	PK observations
A2206: 2 x 10 mg/kg i.v. q3w	28	497	55	442
F2306: 3 x 10mg/kg i.v. q2w + 150 mg s.c. q4w from week 8	191	3470	2766	704
F2306: 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8	183	3286	2612	671
F2306: placebo + 150 mg s.c. q4w from week 16	49	828	488	98
F2306: placebo + 75 mg s.c. q4w from week 16	46	776	457	93
F2306: placebo + 75 mg s.c. q4w from week 24	3	51	24	6
F2312: 4 x 300 mg s.c. q1w + 300 mg s.c. q4w from week 4	87	1785	1551	234
F2312: 4 x 150 mg s.c. q1w + 150mg s.c. q4w from week 4	89	1110	878	232
F2312: 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4	78	977	773	204
F2312: placebo + 150 mg s.c. q4w from week 16	1	12	3	2
TOTAL	755	12792	9607	2686

In general, the PK characteristics of SEK when administered to adult patients with active PsA were highly similar to those observed in other adult patient cohorts with autoimmune disease such as PSOR and RA; and are consistent with the expectations of an IgG antibody interacting with a soluble target (IL-17A). The following is a summary of the main PK findings in the 3 PsA clinical studies that collected serum for PK analysis.

Bioavailability

Following SC administration, SEK has an average absolute bioavailability of 85% in patients with PsA, which is similar but slightly higher to the bioavailability of SEK in the PSOR cohort (73%).

Dose proportionality

At week 4 in Study F2312 (i.e. at the end of the weekly SC loading regimen), the mean trough serum concentrations of SEK increased in a dose proportional manner with the 75 mg dose arm

achieving a level of 24.9 µg/mL, the 150 mg dose group achieving a level of 47.1 µg/mL and the 300 mg arm showing a level of 98.4 µg/mL. At the week 24 visit when SEK exposure was close to steady state, the mean concentrations of SEK remained consistent with dose proportionality being 10.6 µg/mL (inter-subject variability CV 53.5%) in the SEK 75 mg dose group, 19.0 µg/mL (inter-subject variability CV 51.8%) in the SEK 150 mg arm and 38.8 µg/mL (inter-subject variability CV 44.1%) in the SEK 300 mg dose group.

Volume of distribution

The mean volume of distribution in a typical PsA patient weighing 84 kg was estimated to be 6.1 L, which suggests that SEK undergoes limited distribution to peripheral body compartments.

Excretion

Results from the PK modelling report indicate that SEK has a slow mean systemic clearance of 0.19 L/day (with 32.5% CV inter-patient variability) in adult patients with active PsA, and that clearance was both dose and time-independent. PK modelling also indicated that the $t_{1/2}$ was 25 days in PsA subjects with an inter-patient variability CV of 27.5%.

Population PK data for proposed SEK dose in PsA

As summarised in Table 4, the PK modelling report identified that the C_{max} of SEK 150 mg given by SC injection at steady state was 31 ± 10.6 µg/mL in adult patients with active PsA, which is >2-fold higher than that observed after the first dose (14.6 ± 3.78 µg/mL). C_{max} occurred between 5 to 7 days following a dosing and the drug has a mean terminal $t_{1/2}$ of 25 days (with inter-patient variability of 27.5%CV). After the initial weekly SC dosing during the first month of treatment, the time to reach the maximum concentration was between 30 and 35 days and steady state was reached following 20 weeks of therapy with monthly dosing regimens. Based on simulations using weekly SC loading and maintenance therapy every 4 weeks with 150 mg injections, SEK minimal concentrations at steady state ($C_{min,ss}$) were 19.1 µg/mL and the average concentration at steady state ($C_{av,ss}$) were 24.4 µg/mL.

Table 4: PK Metrics for PsA Model using Proposed 150 mg SC Regimen used in Phase 3 Studies.

	Mean	std	%CV	Range (90%)
Cmin at Week 24 [µg/mL]	20	8.98	44.9	[8.89 – 35.9]
Cmin,ss [µg/mL]	19.1	8.31	43.5	[8.49 – 33.6]
Cav,ss [µg/mL]	24.4	7.67	31.4	[13.3 – 43.1]
AUCtau,ss [day·µg/mL]	682	214.9	31.5	[371 – 1208]
Cmax,ss [µg/mL]	31	10.6	34.2	[16.9 – 50]
Tmax,ss [day]	6.22	0.74	11.9	[5 – 7]
Cmax,overall [µg/mL]	60.4	16.9	28	[36.1 – 89.9]
Tmax,overall [day]	32.47	0.71	2.19	[31 – 34]
Cmax,single dose [µg/mL]	14.6	3.78	25.9	[9.04 – 21.3]
Tmax,single dose [day]	5.99	0.1	1.67	[6 – 6]
Terminal half-life [day]	24.6	6.76	27.5	[15.8 – 38]

Source: [AIN457 in PsA – PK modeling report]. Cmax,overall is the highest concentration during treatment, reached after the 5th dose at Day 28. std is standard deviation.

Table 5 summarises the simulated PK parameters for the proposed 300 mg SC dosing regimen in PsA, which the sponsor is requesting to register in 2 subsets of PsA patients (i.e. those with a history anti-TNF-IR and those with concurrent moderate severity PSOR). The 300 mg dose shows serum SEK concentrations and AUC profiles that are approximately 2-fold higher than the 150 mg SC dose regimen, which is to be expected. However, other PK parameters such as clearance, T_{max} and inter-individual variability are similar between 2 proposed doses of SEK in PsA subjects.

Table 5: PK Metrics for PsA Model using Proposed 300 mg SC Regimen used in Phase 3 Studies.

	Mean	std	%CV	Range (90%)
Cmin at Week 24 [µg/mL]	40	18	45	[17.4 – 71.7]
Cmin,ss [µg/mL]	38.3	16.6	43.3	[17 – 67.2]
Cav,ss [µg/mL]	48.7	15.3	31.4	[26.5 – 86.3]
AUCtau,ss [day·µg/mL]	1364	429.7	31.5	[742 – 2415]
Cmax,ss [µg/mL]	62.1	21.1	34	[33.8 – 99.9]
Tmax,ss [day]	6.2	0.74	11.9	[5 – 7]
Cmax,overall [µg/mL]	120	33.9	28.1	[72.3 – 180]
Tmax,overall [day]	32.5	0.71	2.18	[31 – 34]
Cmax,single dose [µg/mL]	29.3	7.56	25.8	[18.1 – 42.6]
Tmax,single dose [day]	5.99	0.1	1.67	[6 – 6]
Terminal half-life [day]	24.6	6.76	27.5	[15.8 – 38]

Source: [AIN457 in PsA – PK modeling report]. Cmax,overall is the highest concentration during treatment, reached after the 5th dose at Day 28. std is standard deviation.

Covariate factors in PK model

In the PsA population, the covariate search algorithm identified 2 potentially significant covariate factors influencing SEK clearance: race (Asian versus non-Asian) and subject weight. The effect of subject weight and race on SEK clearance will be discussed below. Gender, age, anti-TNF status, concomitant use of MTX, baseline PASI and DAS28 scores and time since first diagnosis were not identified as significant factors. There was a trend for altered SEK clearance with extreme values of baseline CRP but this did not reach the pre-specified >20% change from the reference parameter.

Effect of loading and maintenance regimens

Using simulated SEK exposure (AUC) from the SC and IV loading regimens investigated in the 3 PsA studies, the following 4 key observations can be concluded:

- Given the linear kinetics of SEK, at steady state, the 300 mg dose yields twice the exposure levels of the 150 mg dose, which in turn produces twice the exposure of the 75 mg SC dose,
- Comparable SEK exposure is seen between the 150 mg SC regimen (without loading) and the 75 mg SC regimen (with loading) up until week 12,
- The 150 mg SC posology (without loading) reaches comparable SEK exposure levels to the 150 mg SC regimen following loading after week 20, and
- The IV loading regimens show high initial peaks in serum SEK concentrations while the SC loading regimens produce a slower build up which results in exposure levels at week 24 being comparable between the IV and SC dosing regimens.

4.2.3.4. Ankylosing spondylitis

For the PK analysis in AS, a total of 484 subjects contributed data (53 subjects in Study A2209, 294 patients in Study F2305 and 137 subjects in Study F2310). Table 6 lists all the treatment groups included in the PK analysis for AS, as well as their received treatment and PK observations. A total of 101 records (affecting 82 subjects) were excluded from the PK analysis, mainly because blood collections were taken outside of the scheduled visit time window (94 records affecting 75 subjects). In addition, a total of 622 PK observation records had serum concentrations of SEK below the LLOQ. This included 600 samples collected before any active study treatment was commenced and 22 of these records occurred after drug dosing had occurred.

Table 6: Summary of Treatment Groups and the PK Analysis Set for Ankylosing Spondylitis.

Group	N	records	active doses	PK observations
A2209: 2 x 0.1 mg/kg i.v. q3w	12	220	24	196
A2209: 2 x 1 mg/kg i.v. q3w	12	223	24	199
A2209: 2 x 10 mg/kg i.v. q3w	29	542	57	485
F2305: 3 x 10 mg/kg q2w + 150 mg s.c. q4w from week 8	119	2127	1692	435
F2305: 3 x 10 mg/kg + 75 mg s.c. q4w from week 8	116	2111	1682	429
F2305: placebo + 150 mg s.c. q4w from week 16	28	473	275	58
F2305: placebo + 75 mg s.c. q4w from week 16	28	474	278	56
F2305: placebo + 150 mg s.c. q4w from week 24	1	17	8	2
F2305: placebo + 75 mg s.c. q4w from week 24	2	34	16	4
F2310: 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4	69	671	533	138
F2310: 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4	68	662	526	136
TOTAL	484	7554	5115	2138

In general, the PK characteristics of SEK when administered to adult patients with active AS were highly similar to those observed in other adult patient cohorts with autoimmune disease such as PSOR and RA; and are consistent with the expectations of an IgG antibody interacting with a soluble target (IL-17A). The following is a summary of the main PK findings in the 3 AS clinical studies that collected serum for PK analysis.

Bioavailability

Following SC administration, SEK has an average absolute bioavailability of 79% in patients with AS, which is similar to the bioavailability of SEK in healthy Japanese subjects (77%). The estimate of bioavailability in AS patients is consistent with that seen with other IgG1 monoclonal antibodies.

Dose Proportionality

At week 4 in Study F2310 (i.e. at the end of the weekly SC loading regimen), the mean trough serum concentration of SEK was 2-fold higher in the 150 mg dose arm (52.9 µg/mL) compared with the 75 mg arm (25.4 µg/mL), which is consistent with dose proportionality. At week 52 when SEK exposure was at steady state, the mean concentrations of SEK remained consistent with showing dose proportionality being 10.8 µg/mL (inter-subject variability CV 47.8%) in the SEK 75 mg dose group and 20.7 µg/mL (inter-subject variability CV 41.7%) in the SEK 150 mg arm.

Volume of distribution

The mean volume of distribution in a typical AS patient weighing 77 kg was estimated to be 5.5 L, which suggests that SEK undergoes limited distribution to peripheral body compartments.

Excretion

Results from the PK modelling report indicate that SEK has a slow mean systemic clearance of 0.16 L/day in adult patients with active AS, and that clearance was both dose and time-independent. Individual studies in the target population estimated that following IV administration of SEK at doses ranging from 0.1 to 10 mg/kg, clearance ranged from 0.14 to 0.21 L/day (Study A2209). PK modelling also indicated that the $t_{1/2}$ was 26 days in AS subjects. Individual studies conducted in the target population (Studies A2209, F2305 and F2310)

identified that the $t_{1/2}$ of SEK ranged from between 25.7 and 32.4 days following IV infusions of SEK with doses ranging from 0.1 to 10 mg/kg, and between 22 and 33.6 days following SC doses of SEK 75 to 150 mg.

Population PK data for proposed SEK dose in AS

As summarised in Table 7, the PK modelling report identified that the C_{max} of SEK 150 mg given by SC injection at steady state was 34.1 ± 12.1 µg/mL in adult patients with active AS, which is approximately 2-fold higher than that observed after the first dose (16.1 ± 4.57 µg/mL). C_{max} occurred between 5 to 6 days following a dosing and the drug has a mean terminal $t_{1/2}$ of 26 days (with inter-patient variability of 27%CV). After the initial weekly SC dosing during the first month of treatment, the time to reach the maximum concentration was between 31 and 34 days and steady state was reached following 20 weeks of therapy with monthly dosing regimens. Based on simulations using weekly SC loading and maintenance therapy every 4 weeks with 150 mg injections, SEK minimal concentrations at steady state ($C_{min,ss}$) were 20.8 µg/mL and the average concentration at steady state ($C_{av,ss}$) were 25.8 µg/mL.

Table 7: PK Metrics for AS Model using Proposed 150 mg SC Regimen used in Phase 3 Studies.

	Mean	std	%CV	Range (90%)
Cmin at Week 24 [µg/mL]	24.7	11	44.5	[10.9 – 46.2]
Cmin,ss [µg/mL]	20.8	9.1	43.8	[9.7 – 39]
Cav,ss [µg/mL]	25.8	8.1	31.4	[14.7 – 48.5]
AUCtau,ss [day·µg/mL]	722.9	227.2	31.4	[410 – 1359]
Cmax,ss [µg/mL]	34.1	12.1	35.5	[18.7 – 57.5]
Tmax,ss [day]	6	0.7	11.7	[5 – 7]
Cmax,overall [µg/mL]	64.3	19	29.6	[38.5 – 99.8]
Tmax,overall [day]	32.3	0.64	1.98	[32 – 33]
Cmax,single dose [µg/mL]	16.1	4.57	28.4	[9.65 – 24.2]
Tmax,single dose [day]	5.98	0.14	2.34	[6 – 6]
Terminal half-life [day]	25.7	6.93	27	[17.3 – 39.4]

Source: [AIN457 in AS – PK modeling report]. Cmax,overall is the highest concentration during treatment, reached after the 5th dose at Day 28. std is standard deviation.

Covariate Factors in PK Model

In the AS population, the covariate search algorithm identified 2 potentially significant covariate factors influencing SEK clearance: baseline CRP reading and subject weight. The effect of subject weight on SEK clearance will be discussed below. Gender, age, anti-TNF status, concomitant use of MTX, baseline BASDAI score and time since first diagnosis were not identified as significant factors. There was a trend for altered SEK clearance with extreme values of baseline CRP but this did not reach the pre-specified >20% change from the reference parameter.

Effect of loading and maintenance regimens

Using simulated SEK exposure (AUC) from the SC and IV loading regimens investigated in the 3 AS studies, the following 3 key observations can be concluded:

- Comparable SEK exposure is seen between the 150 mg SC regimen (without loading) and the 75 mg SC regimen (with loading) up until week 12,
- The 150 mg SC posology (without loading) reaches comparable SEK exposure levels to the 150 mg SC regimen following loading after week 20, and
- The IV loading regimens show high initial peaks in serum SEK concentrations while the SC loading regimens produce a slower build up which results in exposure levels at week 24 being comparable between the IV and SC dosing regimens.

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

No formal PK study has been conducted in patients with hepatic impairment as the sponsor states that the majority of IgG elimination occurs via intracellular catabolism.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

Similar to hepatic impairment, no PK data has been collected in patients with renal impairment.

4.2.4.3. Pharmacokinetics according to age

SEK is only proposing registration for use in adult patients and no PK data is available in paediatric patients. Of the 974 patients with active PsA exposed to SEK in the Phase 2-3 clinical studies, a total of 85 subjects were 65 years of age or older and only 4 patients were 75 years of age or older. Of the 571 adult patients with active AS exposed to SEK in the Phase 2-3 clinical studies, a total of 24 subjects were 65 years of age or older and only 3 patients were 75 years of age or older. However, based on the population PK analysis, drug clearance in elderly patients (with either newly proposed treatment indication) and in patients <65 years of age was similar.

4.2.4.4. Pharmacokinetics according to subject weight and race

In both the PsA and AS population PK modelling reports, subject weight was identified as a significant covariate factor influencing the SEK clearance and apparent volume of distribution in an allometric relationship. For subjects with PsA, clearance was estimated to be 0.8 L/day and the central volume of distribution was estimated to be 0.44 L. For adult patients with active AS, clearance was also estimated to be 0.8 L/day and the central volume of distribution was estimated to be 1.2 L. Overall, these results indicate that a doubling of subject body weight could lead up to a nearly 2-fold increase in clearance and distribution volume. These results are consistent with observations for other registered monoclonal antibodies (Zhang et al, 2012).

Table 8: Influence of Covariates upon SEK Clearance in PsA Population PK Model.

	Estimated clearance (L/Day)	%Change from "typical"
"Typical" clearance	*0.17*	*0*
Bodyweight=55 kg	0.12	-28
Bodyweight=120 kg	0.22	32
Baseline CRP=0.7 mg/L	0.15	-11
Baseline CRP=48.6 mg/L	0.19	13
Race=Asian	0.2	20
TNF-α IR	0.19	11

Table 9: Influence of Covariates upon SEK Clearance in AS Population PK Model.

	Estimated clearance [L/Day]	%Change from "typical"
"Typical" clearance	*0.15*	*0*
Bodyweight=53 kg	0.11	-25
Bodyweight=112 kg	0.21	35
Baseline CRP=0.7 mg/L	0.13	-18
Baseline CRP=64 mg/L	0.18	20
TNFα-IR	0.16	8

The PK modelling reports also examined the effect of race (non-Asian versus Asian subjects) on SEK clearance. In the PsA PK database, 100 patients were Asian in the total cohort of 755 subjects. The population PK analysis in PsA showed higher clearance in Asian subjects, which was supported by the model comparing C_{min} values at steady state. Typical steady state C_{min} was 16.3 µg/mL (90% CI 7.1-29 µg/mL) in Asian patients (with the same bodyweight as non-Asian subjects) compared with 20.6 µg/mL (90% CI 9.3-36.1 µg/mL) in non-Asian patients. This

difference did not meet the criteria for being a clinically relevant covariate in the adult PsA population. In the PSOR population PK analysis, Asian subjects had a mean 12.4% higher clearance of SEK than non-Asian subjects. Overall, in both the PsA and PSOR populations, this relatively small difference in SEK clearance is unlikely to be of clinical relevance. Out of 484 patients in the AS PK database, 55 subjects were Asian. The population PK analysis in AS subjects did not identify any statistically significant differences in SEK clearance between the 2 patient subgroups.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

No studies have examined for potential interactions between SEK and other drugs in either the healthy volunteer or the target disease populations. The sponsor states that SEK can be co-administered with other drugs, which patients with autoimmune and immune-mediated diseases commonly ingest. Medications co-administered to these patient populations may include potent low molecular weight immunosuppressant agents with known potential for drug-drug interactions. However, drug-drug interactions between monoclonal antibodies and such low molecular weight drugs were not routinely investigated because hepatic metabolising enzymes such as cytochrome P450 systems are not presumed to be involved in the elimination of monoclonal antibodies. However, several anti-TNF drugs have reported reduced drug clearance when co-prescribed with methotrexate (MTX). The population PK results for SEK use in PsA and AS patient do not identify that low dose oral MTX has an impact of the PK characteristics of SEK.

Clinical implications of in vitro findings

In vitro drug-drug interaction studies with SEK have not been conducted.

4.3. Evaluator's overall conclusions on pharmacokinetics

In the PK summary of this report, the 2 new treatment indications (PsA and AS) will be considered together because the interpretation of the results and conclusions are similar with respect to PK characteristics. Overall, the sponsor has provided a sufficient quantity of new PK data (including serum trough SEK concentrations collected at weeks 4, 16, 24 and 52 in each of the pivotal studies for each treatment indication) in this submission for patients with the additional treatment indications of active PsA and AS. The sponsor is proposing minor changes to the PK section of the current PI to include the new PK data.

The key PK findings for SEK use in adult patients with active PsA or AS are:

- The drug exposure parameters of AUC and C_{max} in both PsA and AS increase in proportion to dose over the range of 0.1 mg/kg to 10 mg/kg when given by IV infusion and from 75 mg to 300 mg when administered by SC injection;
- SEK exhibits first order absorption following SC injection with the estimated bioavailability being 85% in PsA patients and 79% in AS subjects;
- Typical apparent total volumes of distribution in PsA and AS are 6.1 L and 5.5 L, respectively;
- Clearance from the central compartment in typical subjects is 0.19 L/day in PsA (with 32.5% CV) and 0.16 L/day in AS (with 32.8% CV);
- The apparent elimination half-life is 25 days in PsA (with inter-patient variability [CV] of 27.5%) and 26 days in AS (with inter-patient variability [CV] of 27.0%);
- There is no evidence of a time dependent change in SEK PK in the PsA and AS populations;

- In both the PsA and AS populations, the only covariate factor of potential clinical relevance for alteration in clearance and volume of distribution for SEK is subject body weight. Baseline CRP value and prior anti-TNF status did not have a clinically relevant influence on clearance when adjusted for subject weight; and
- Modelling of data in both PsA and AS indicates that loading regimens (IV and SC) increase drug exposure to SEK in the short term (first 12-20 weeks depending on regimen), but there is no additional SEK exposure difference beyond 20-24 weeks of continued therapy.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The ability of SEK to bind and capture circulating IL-17A has been formally validated in several clinical studies involving healthy volunteers and different disease affected populations, such as adult patients with PSOR and rheumatoid arthritis. Many of these trials were previously evaluated in the original PSOR submission (ID: PM-2013-04153-1-4). The PD effect of SEK has been primarily assessed by the measurement of total serum IL-17A. Total IL-17A can be regarded as a biomarker for SEK and is indicative of target engagement. Total IL-17A is defined as free IL-17A plus IL-17A complexed with SEK after drug exposure.

In these 2 submissions, the sponsor has presented additional pharmacodynamic (PD) data in a meta-analysis report evaluating total IL-17A levels in 8 studies (ranging from Phase 1-3). The 8 trials were chosen to cover a broad range of dosing regimens across healthy volunteers and different autoimmune conditions. The 8 studies included the 2 supporting trials key to these submissions. Study A2206 in patients with PsA (n=42) and Study A2209 in patients with AS (n=60) contributed to the meta-analysis data. The other 6 trials contributing to the meta-analysis dataset were Study A1101 (42 healthy Japanese male volunteers), Study A2212 (100 adult PSOR patients), Study A2220 (125 adult PSOR patients), Study A2309 (182 adult PSOR patients), Study F2201 (237 adult patients with active RA despite stable treatment with MTX) and Study F2208 (190 adult patients with active RA). None of the PD studies had deficiencies that excluded their results from consideration. However, in Study 2206, one of the secondary objectives was to assess the PD of SEK in synovial tissues obtained by biopsy of affected joints at baseline and week 6. However, very few patients consented to synovial biopsy (4 in total; 2 received SEK and 2 were in the PBO arm), so no PD analyses of synovial tissue samples was undertaken.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans.

5.2.1. Mechanism of action

The PD effect of SEK is a consequence of its selective, high affinity binding to human IL-17A, blocking the interaction of this cytokine to its receptor. Consequently, inhibition of IL-17A signalling results. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses, however, IL-17A also plays a key role in the pathogenesis of PsA and AS. IL-17A is a homodimer and belongs to the IL-17 cytokine family that includes 6 members. IL-17A shares close similarities with IL-17F, the only other IL-17 family member secreted by Th-17 cells. Recently, an IL-17A/IL-17F heterodimer (referred to as IL-17AF) with biological activity intermediate between IL-17A and IL-17F has been described but the contribution of the IL-17AF heterodimer to human inflammatory and autoimmune disease remains unclear. IL-17A is not only produced by Th-17 cells, but also cells of the innate immune system, such as macrophages, mast cells and neutrophils. Furthermore, the widespread

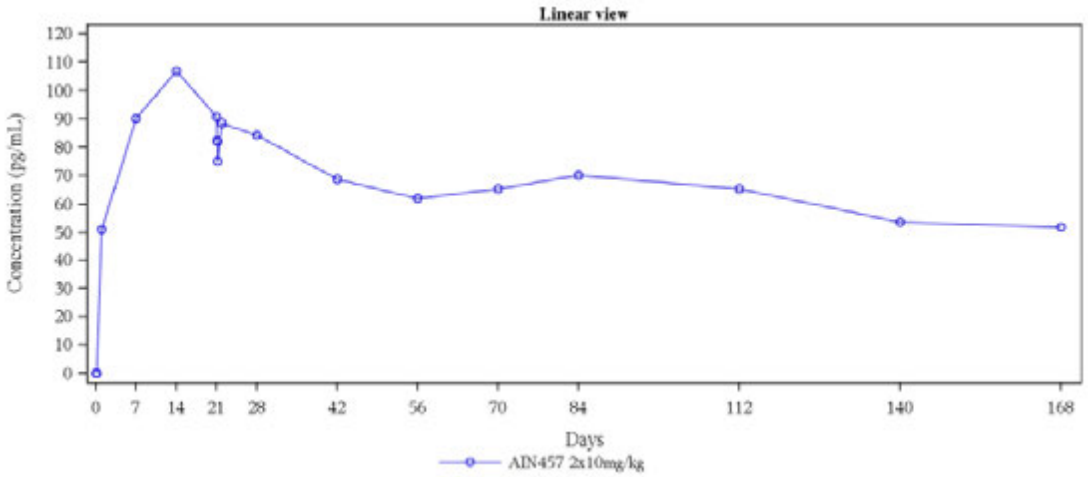
expression of the IL-17 receptors enables IL-17A to act on a variety of cell types including epithelial cells (like keratinocytes), dendritic cells, macrophages, fibroblasts, osteoblasts and endothelial cells. Through induction of multiple downstream mediators, IL-17A exhibits a wide spectrum of effector functions ranging from protective to pathologic immune response. Its main physiologic roles in host defence are protection against extracellular bacteria and fungi. IL-17A is a potent mobiliser of neutrophils and is important in neutrophil homoeostasis. As it contributes to neutrophil recruitment to sites of infection, IL-17A facilitates clearance of certain bacteria. A prominent role of IL-17A has also been postulated for protection against mucosal fungi, such as *Candida albicans*.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

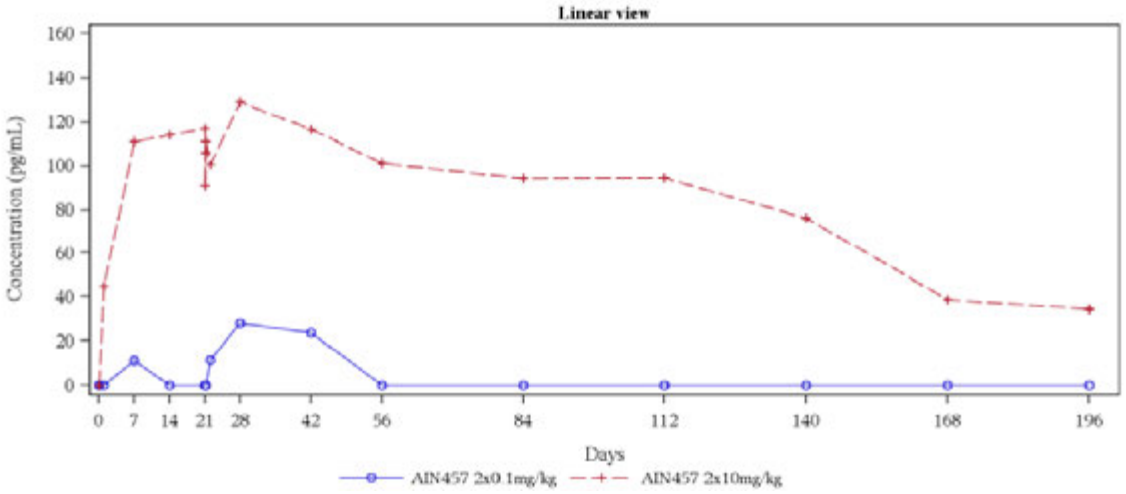
Study A2206 examined total IL-17A levels up to day 168 in adult patients with active PsA following 2 IV infusions of SEK 10 mg/kg given 3 weeks apart (baseline and week 3) – refer to Figure 1. Patients with PsA who received IV SEK 10 mg/kg achieved a median total IL-17A concentration of 107 pg/mL at 2 weeks after IV administration. There was marked inter-individual variability in total IL-17A levels after SEK with day 21 levels ranging from 20 to almost 400 pg/mL.

Figure 1: Median Total IL-17A Concentrations over Time in Study A2206.



Study A2209 examined total IL-17A levels up to day 196 in adult patients with active AS following 2 IV infusions of SEK given 3 weeks apart (baseline and week 3) – refer to Figure 2. Two doses of SEK were investigated for PD effects in this study – 0.1 mg/kg and 10 mg/kg. The AS data shows the maximal concentration of total IL-17A and the total exposure of total IL-17A increased with SEK dose, which is identical to what has been observed in healthy volunteers and patients with PSOR. Patients who received IV SEK 10 mg/kg achieved total IL-17A concentrations between 100 and 130 pg/mL compared to <30 pg/mL in those administered IV SEK 0.1 mg/kg. Peak concentrations of total IL-17A were reached 2-4 weeks after IV administration of SEK. There was marked inter-individual variability in total IL-17A levels after SEK with day 21 levels ranging from 40 to 380 pg/mL in the 10 mg/kg dose group and from 5 to >200 pg/mL in the 0.1 mg/kg arm.

Figure 2: Median Total IL-17A Concentrations over Time in Study A2209.



5.2.2.2. Secondary pharmacodynamic effects

The effect of SEK on immunogenicity (i.e. formation of anti-drug antibodies) will be discussed elsewhere in this report. The effect of SEK on neutrophil counts in the blood of treated patients with PsA and AS will be discussed elsewhere. The effect of SEK upon reducing serum inflammatory markers (mainly, CRP readings) will be discussed in the efficacy section of this report.

5.2.3. Time course of pharmacodynamic effects

In all studied populations (healthy volunteers and various disease populations, including PsA, PSOR and AS), total IL-17A levels rise to a plateau over the first 2 weeks following the first dose of SEK. The onset of this effect (i.e. rise in serum total IL-17A levels) is seen as early as 2-7 days following SEK administration. The time-concentration profile of total IL-17A following SEK administration parallels the elimination half-life of SEK itself, which indicates that IL-17A clearance occurs exclusively in its bound form to SEK.

The Phase 2-3 study data in both PsA and AS indicates that SEK exerts its secondary PD effects upon reducing serum inflammation (i.e. serial CRP values) over a time course of 1-2 weeks following drug administration.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The sponsor also included an exploratory analysis of SEK exposure-response of efficacy and adverse events on patients with PsA and AS. The analysis was limited to SC loading regimens tested in Studies F2310 (subjects with AS) and F2312 (patients with PsA). In both treatment indications, there was a trend for improved efficacy response (e.g. using ASAS and BASDAI criteria in AS and DAS-28 score in PsA) with higher C_{min} values but the exposure-response for efficacy parameters flattened at a C_{min} level higher than 25 µg/mL, which corresponds approximately to the mean C_{min} achieved at week 16 with SEK 150 mg SC injections. There was no apparent relationship between High drug exposure levels and the incidence of adverse effects (overall, serious adverse events and particular types of infection).

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

No specific studies have been conducted examining whether there were genetic-, gender- or age-related differences in PD response following treatment with SEK.

5.2.6. Pharmacodynamic interactions

In the previous PSOR submission, the effect of SEK upon vaccinations against influenza and Neisseria meningitidis serogroup C was evaluated in Study A2224. In this trial, a total of 50

healthy subjects received treatment with 150 mg of SEK administered by SC injection. The study showed that SEK had no detrimental effect on the generation of protective antibody titres following vaccination with either vaccine. No new information regarding vaccination response has been provided in these submissions.

5.3. Evaluator's overall conclusions on pharmacodynamics

In the PD summary of this report, the 2 new treatment indications (PsA and AS) will be considered together because the interpretation of the results and conclusions are similar with respect to PD characteristics. The sponsor has provided additional PD data in the form of a meta-analysis report evaluating total IL-17A levels in 8 studies, including 1 study in each newly proposed treatment indication in this submission. The sponsor is proposing minor changes to the PD section of the current PI to include the new PD data.

The key PD findings for SEK use in adult patients with active PsA or AS are:

- Maximal median concentrations of total IL-17A and the total exposure of total IL-17A increased with SEK dose (as seen in the AS Study 2209 plus other trials);
- Median serum concentrations of total IL-17A ranged between 107 and 130 pg/mL with the dosing regimen of 2 IV doses of SEK 10 mg/kg (given 3 weeks), whereas concentrations remained < 30 pg/mL with 2 IV doses of SEK 0.1 mg/kg;
- Total IL-17A concentrations increased over several weeks following 10 mg/kg IV dosing and peak levels were reached after 2-4 weeks;
- Considerable inter-subject variability was observed in total IL-17A profiles across patients with AS and PsA;
- Total IL-17A concentrations lag behind the peak serum concentrations of SEK after IV dosing; and
- There was a trend for improved efficacy response in both AS and PsA with higher Cmin values but the exposure-response for efficacy parameters flattened at a Cmin level higher than 25 µg/mL, which corresponds approximately to the mean Cmin achieved at week 16 with SEK 150 mg SC injections.

6. Dosage selection for the pivotal studies

6.1. Psoriatic arthritis

To select the SEK dose regimens for further investigation in the pivotal Phase 3 PsA program, input from 4 sources of data were utilised: data from the proof-of-concept study in PsA (A2206), data from the Phase 2, dose-ranging trial in RA (Study F2201), dose-efficacy predictions from the Phase 2-3 studies in moderate to severe PSOR (i.e. the PK and PASI response modelling report) and the dose-exposure predictions from the population PK modelling reports of SEK. Study A2206 demonstrated that 2 IV doses of SEK 10 mg/kg was efficacious in improving the signs and symptoms of PsA, but no maintenance dose was evaluated in this short-term (primary efficacy assessment of ACR20 response at week 6), proof-of-concept trial. Maintenance doses in the Phase 3 PsA studies were selected based on the results from Study F2201 in RA. Study F2201 was Phase 2, dose-ranging trial involving 236 adult patients with active RA. The trial examined 4 doses of SEK (25 mg, 75 mg, 150 mg and 300 mg) administered by SC injection versus PBO therapy. Study treatment was given at baseline, and then at weeks 4, 8 and 12. The primary endpoint of the trial (ACR20 response rate at week 16) was not achieved. However, the Phase 2 RA trial suggested that the 75 mg and 150 mg SC regimens could be efficacious for the

longer term control of PsA symptoms. The PSOR trials identified that a higher dose of SEK (300 mg injections) may be required to achieve satisfactory clinical benefit. In addition, dosing from the PSOR registration trials supported the decision to examine SEK treatment regimens involving loading doses (IV and SC) to potentially provide a faster onset of arthritic symptom relief.

Both of the pivotal Phase 2 PsA trials were placebo (PBO)–controlled for the first 16-24 weeks. About 20% of PBO treated patients at week 16 were considered responders and continued with PBO up to week 24. The TGA Delegate requested a rationale for the absence of active comparator, especially considering that established and effective treatment options are registered and available for this indication in Australia. The Phase 3 data for SEK did not examine anti-TNF therapy as an active comparator as "may be required" according to the TGA adopted EU guideline. However, there is no precedent for an approval of a non-anti-TNF drug in PsA. As blockade of IL-17A presents a novel approach to the treatment of PsA, the sponsor states that it is important to establish efficacy for this new mechanism of action in patients who have failed anti-TNF drugs, for whom currently no other biologic therapy is available in Australia. The goal of the Phase 3 PsA program with SEK was to demonstrate efficacy and safety in both patients who had previously been exposed to anti-TNF drugs and those who were anti-TNF naïve, which is an acceptable real life experience in Australian practice. In addition, most registration trials with anti-TNF did not include patients who had previously failed biologic therapy. The Phase 3 SEK PsA studies included 31% of patients with the highest unmet treatment need, i.e. they have failed anti-TNF therapy.

6.2. Ankylosing spondylitis

The data from 2 dose-ranging Phase 2 studies, 1 conducted in adult patients with AS (Study A2209) and the other in adult patients with RA (Study F2201), were primarily used to define the dosing regimens of SEK to be examined in the Phase 3 AS program. Study A2209 demonstrated that 2 IV doses of SEK 10 mg/kg was efficacious in improving the signs and symptoms of AS, but no maintenance dose was evaluated in this short-term (primary efficacy assessment at week 6), proof-of-concept trial. Maintenance doses in the Phase 3 AS studies were selected based on the results from Study F2201 in RA. Study F2201 was Phase 2, dose-ranging trial involving 236 adult patients with active RA. The trial examined 4 doses of SEK (25 mg, 75 mg, 150 mg and 300 mg) administered by SC injection versus PBO therapy. Study treatment was given at baseline, and then at weeks 4, 8 and 12. The primary endpoint of the trial (ACR20 response rate at week 16) was not achieved. The Phase 2 RA trial suggested that the 75 mg and 150 mg SC regimens could be efficacious for the longer term control of AS symptoms, and that a higher dose of SEK, such as 300 mg injections, would not confer any additional clinical benefit. In addition, dosing from the PSOR registration trials supported the decision to examine SEK treatment regimens involving loading doses (IV and SC) to potentially provide a faster onset of arthritic symptom relief.

Both of the pivotal Phase 3 AS trials were PBO-controlled for the first 16-24 weeks. The TGA delegate requested a rationale for the absence of an active comparator given that there are registered treatment options available in Australia, in particular, anti-TNF therapy for moderately to severely active AS that has failed to respond to NSAID and exercise therapy. However, the TGA adopted EU guideline suggests that an active comparator "may be required" but does not mandate the issue.

The goal of the Phase 3 AS clinical program for SEK was to reflect the contemporary AS population, which involves the inclusion of a mixture of anti-TNF-IR patients as well as anti-TNF naïve subjects.

7. Clinical efficacy

7.1. Indication 1: psoriatic arthritis

7.1.1. Pivotal efficacy studies

7.1.1.1. Studies F2306 (FUTURE-1) and F2312 (FUTURE-2)

Study design, objectives, locations and dates

There were 2 pivotal Phase 3 trials in support of the application for the treatment of PsA with SEK. Both of the Phase 3 studies were of similar design - randomised, double-blind, parallel-group, placebo-controlled trials in adult patients with active PsA. The main differences between the 2 pivotal Phase 3 studies was the use of an IV loading dose in Study F2306 versus a SC loading dose in Study F2312. In addition, Study F2312 also included a third dose of SEK for evaluation (300 mg). Both of the Phase 3 trials examined the effect of SEK 75 mg and 150 mg injections.

Because the Phase 3 studies are highly similar in design and conduct, they will be considered together in this report with their important differences highlighted and results presented independently. Both of the Phase 3 studies had a screening phase (up to 4 weeks in Study F2306 and up to 10 weeks in Study F3212) to assess eligibility prior to randomisation. In this submission, the pivotal clinical efficacy data up to week 24 was included for both studies,[2] but the trial schema was for a total treatment period of 2 years in Study F2306 and up to 5 years in Study F2312. In both trials, clinical efficacy and safety assessments were performed at baseline; weeks 1, 2 and 4; and every 4 weeks thereafter up until week 52. Study F2306 also collected radiographic data at baseline, as well as weeks 24 and 52 in support of the claim to reduce the rate of progression of joint damage.

In Study F2306 (FUTURE-1), eligible patients were to be equally randomised at baseline into 1 of 3 treatment groups. The first 2 groups were to receive IV SEK 10 mg/kg at baseline, week 2 and week 4. At week 8, one of the SEK treatment groups continued with a SC maintenance regimen of SEK 75 mg injected every 4 weeks and the other SEK treatment arm received a SC maintenance regimen of 150 mg every 4 weeks. The placebo (PBO) treatment group were to receive IV placebo at baseline, week 2 and 4; followed by SC placebo injections every 4 weeks starting at week 8.

In Study F2312 (FUTURE-2), eligible patients were to be equally randomised at baseline into 1 of 4 treatment groups: SEK 75 mg, SEK 150 mg, SEK 300 mg and PBO injections. All injections were given by SC administration at baseline; weeks 1, 2, 3 and 4; and then every 4 weeks thereafter.

The design of both Phase 3 studies allowed for Early Escape (EE) in PBO treated patients demonstrating insufficient improvement. This is appropriate for ethical reasons. At week 16, subjects with <20% improvement from baseline in both tender and swollen joint counts were eligible to enter EE in a blinded manner. In Study F2306, subjects in the PBO group who met EE criteria were re-randomised 1:1 to receive blinded therapy with either SEK 75 mg injections every 4 weeks or 150 mg injections every 4 weeks (by SC administration). Subjects already receiving SEK who met the EE criteria at week 16 continued to receive their originally assigned therapy in a blinded fashion. At week 24, all remaining subjects in the PBO cohort were re-randomised 1:1 to receive either SEK 75 mg injections every 4 weeks or 150 mg injections every 4 weeks (by SC administration).

The same EE criteria applied in Study F2312. Subjects randomised into the PBO group of this trial who met EE criteria were re-randomised 1:1 to receive blinded therapy with either SEK

[2] The sponsor provided the 52-week data for Study F2306.

150 mg injections every 4 weeks or 300 mg injections every 4 weeks (by SC administration). Subjects already receiving SEK who met the EE criteria at week 16 continued to receive their originally assigned therapy in a blinded fashion. At week 24, all remaining subjects in the PBO cohort were re-randomised 1:1 to receive either SEK 150 mg injections every 4 weeks or 300 mg injections every 4 weeks (by SC administration).

The primary objective of the Phase 3 PsA study program was to demonstrate that the efficacy of SEK was superior to PBO at 24 weeks in treating the symptoms and signs of active PsA in adult patients. The secondary efficacy objectives of the study program included the assessment of the effects of SEK upon physical functioning, skin outcomes, health related Quality-of-Life (QOL) and X-ray damage.

Study F2306 was conducted at 112 investigator sites in 19 countries in Europe, North and South America and the Asia-Pacific region, which includes Australia, Singapore, Thailand and the Philippines. The countries with the highest number of active sites in Study F2306 were USA (27 centres), Germany (14 centres), Philippines (9 centres) and Argentina (8 centres). All other involved countries had 2-6 active sites (including 2 centres in Australia). Study F2306 was conducted between September 2011 and October 2013 (i.e. last patient's week 52 visit for interim analysis). A total of 3 protocol amendments were implemented in this trial. The first amendment was instituted before the commencement of patient enrolment, and the other 2 amendments occurred after. The amendments contained clarifications about the screening assessment, guidance on how missing data would be handled in the data analysis and an additional description about the statistical analysis plan. None of the amendments had the potential to have significantly impacted on the integrity of the results.

Study F2312 was conducted in 76 investigator sites in 10 countries in Europe (including 10 centres each in UK and Russia, and 9 sites in Germany), North America (22 centres in USA and 6 sites in Canada), Australia (4 centres) and Thailand (2 centres). The study was conducted between April 2013 and May 2014 (i.e. last patient's week 24 visit for interim analysis). Only 1 protocol amendment was implemented. This occurred after enrolment into the trial was complete, but before database lock. The amendment expanded the statistical hierarchy of efficacy endpoint testing to match Study F2306 and provided additional detail about the statistical analysis plan to examine for response according to prior anti-TNF status. The amendment did not significantly impair the integrity of the results.

Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 18 years of age with a diagnosis of PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and with symptoms for at least 6 months. Subjects had to have active disease at baseline as evidenced by ≥3 swollen and ≥3 tender joints. All subjects were required to have active plaque psoriasis with at least 1 qualifying psoriatic skin lesion ≥2 cm, or nail changes consistent with psoriasis, or a documented history of plaque psoriasis. Rheumatoid factor testing and anti-cyclic citrullinated peptide (anti-CCP) antibodies were to be negative.

The eligibility criteria for Studies F2306 and F2312 required subjects to have active PsA despite current or previous treatment with NSAID, conventional DMARD therapy and/or anti-TNF drugs. Study F2306 planned to enrol 30% of subjects with therapeutic failure to anti-TNF drugs (maximum of 3 agents) to ensure a representative PsA population was examined. Anti-TNF-IR (inadequate responder) status was defined as patients having active disease despite treatment with TNF inhibitors for at least 3 months at a stable dose or for at least 1 dose in the situation of lack of tolerance. Study F2312 aimed to have 40% of randomised subjects as being anti-TNF-IR (maximum of 3 prior anti-TNF drugs).[3] Biological therapy, other than with anti-TNF drugs, was an exclusion criterion in both studies. Prior treatment with anti-TNF drugs was to have been

[3] The study specified that no more than 40% could be TNF-IR.

ceased at least 8-10 weeks prior to randomisation, with the exception of etanercept whereby 4 weeks was deemed acceptable.

Concomitant treatment with MTX (up to 25 mg/week) was allowed if the dose and route of administration had been stable for at least 4 weeks prior to randomisation. Patients receiving MTX were required to be taking folic acid supplementation. Patients taking DMARDs other than MTX were required to cease such therapy for at least 4 weeks prior to randomisation (or 8 weeks if taking leflunomide and it is not removed by cholestyramine washout). In both of the Phase 3 studies, the concomitant use of oral corticosteroids (CS) was permitted for subjects taking stable doses (prednisone [or equivalent] <10 mg/day) for at least 2 weeks prior to randomisation. The dose of CS was to remain stable up to week 24. No CS injections (intra-articular or parenteral) were permitted within 4 weeks of randomisation. However, low potency topical CS was allowed as background therapy for psoriasis affecting the face, scalp and genital area. Concomitant NSAID was also permitted during both trials, provided subjects were on a stable dose for at least 4 weeks prior to randomisation. Patients taking any high potency opioid analgesic drugs (e.g. hydromorphone, methadone or morphine) were excluded.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A past history of substance abuse within the last 6 months, infection requiring treatment within 2 weeks, and a history of blood donation or loss within 8 weeks prior to screening were to be excluded. A history of malignancy (except for excised basal cell skin cancers or actinic keratosis, colonic polyps that have been removed, or cervical carcinoma in situ successfully treated by surgery) was also an exclusion criterion.

Subjects were screened for Hepatitis B and C, HIV as well as latent Tuberculosis (TB) at baseline. The screening for latent TB involved either skin testing with PPD or QuantiFERON TB-Gold testing. Subjects with active TB were excluded, but those with latent TB could be included after treatment according to local country guidelines was initiated. All patients were required to have a chest X-ray within 12 weeks prior to screening.

Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases >2 x Upper Limit Normal (ULN), total serum bilirubin >27 µmol/L, serum creatinine >1.5 mg/dL, total white blood cell count <3.0 x 10^9/L, platelet count <100 x 10^9/L and haemoglobin <8.5 g/dL.

Study treatments

Study F2306

In Study F2306, subjects were randomised in a 1:1:1 ratio to receive SEK 75 mg, SEK 150 mg or PBO injections. The 2 SEK treatment groups received IV SEK 10 mg/kg at baseline, week 2 and week 4. At week 8, one of the SEK treatment groups continued with a SC maintenance regimen of SEK 75 mg injected every 4 weeks and the other SEK treatment arm received a SC maintenance regimen of 150 mg every 4 weeks. The PBO arm received matching IV placebo infusions at baseline, week 2 and 4; followed by SC PBO injections every 4 weeks starting at week 8. At week 16 or 24, all continuing PBO treated subjects were re-randomised and switched to either maintenance dose regimen of SEK.

All study treatment with SEK (IV loading doses as well as the SEK 75 mg and 150 mg SC injections) was supplied as a lyophilised cake powder for solution presented in vials containing 150 mg of drug. The vials contained a 20% overflow to allow complete withdrawal of the labelled amount of SEK. The loading IV therapy (SEK and PBO infusion) was administered in 100 mL of 0.9% sodium chloride. The SC drug treatment was injected with a 27G needle (1 injection per visit). The sponsor has not commented on whether or not minor differences in the presentation and viscosity between the SEK and PBO SC injections were apparent. Patients did not self-administer SC therapy in Study F2306.

The only concurrent non-biological DMARD treatment permissible during Study F2306 was MTX ≤ 25 mg weekly. The dose of continued MTX had to be stable for at least 4 weeks prior to baseline. Patients were also able to continue with low dose CS (maximum oral dose of 10 mg/day of prednisone or equivalent) if they had been receiving a stable dose for at least 2 weeks prior to baseline. Similarly, NSAID (including COX-2 inhibitors) could be continued if these treatments were stable for at least 2 weeks prior to baseline. Analgesic medications (including paracetamol) were permitted except for ad hoc use within 24 hours prior to any scheduled study assessments. No change in concurrent NSAID, CS or MTX dose was permitted in the first 24 weeks of the study, except for documented safety reasons.

Study F2312

In this trial, eligible patients were equally randomised at baseline into 1 of 4 treatment groups: SEK 75 mg, SEK 150 mg, SEK 300 mg and PBO injections. All injections were given by SC administration at baseline; weeks 1, 2, 3 and 4; and then every 4 weeks thereafter. To maintain blinding, 3 matching injections (all supplied in prefilled syringes) were given SC to all subjects at each visit – 2 x 1.0 mL and 1 x 0.5 mL injections. Three simultaneous SC injections were necessary as SEK was only provided in 2 syringe sizes (0.5 mL containing SEK 75 mg and 1.0 mL containing SEK 150 mg). There was no unique syringe presentation for SEK 300 mg therapy.

All study treatment was to be self-administered under direct supervision throughout the study. However, investigator staff was allowed to administer injections to patients who were not capable of self-administration. Less than half of all subjects self-administered study treatment on at least 1 occasion in the first 16 weeks – refer to Table 10. A higher proportion of subjects in the SEK 75 mg group self-administered therapy (58%; 58/100) compared to the other 3 treatment groups (36-48%). Overall, self-administration of study treatment in Study F2312 was relatively low at 30-44% of study visits up to week 16.

Table 10: Self-Administration of Study Treatment up to Week 16 in Study F2312.

Treatment group	Number (%) of patients who self-administered[1]	% of visits with self-administration[2]
Any AIN457 75 mg (N = 99)	44 (44.44)	30.04
Any AIN457 150 mg (N = 100)	58 (58.00)	44.37
Any AIN457 300 mg (N = 100)	36 (36.00)	29.09
Any AIN457 (N=299)	138 (46.15)	34.57
Placebo (N = 98)	47 (47.96)	37.78

- Dose administration data for placebo non-responders at Week 16 were shown under placebo treatment group.

[1] Patient was counted only once under the treatment group even if the patient has multiple (secukinumab and placebo) self-administrations during the treatment period.

[2] Multiple (active and dummy) injections in a visit were considered as one injection under that visit.

Percentage is calculated as: (# visits with self-administration up to Week 16 / # total visits with dose administration up to Week 16) * 100.

AIN457=SEK

Efficacy variables and outcomes

The main efficacy variables were:

- American College of Rheumatology (ACR) response criteria,
- Psoriasis Area and Severity Index (PASI), and
- van der Heijde - modified Total Sharp Score (vdH-mTSS).

The primary efficacy outcome in both Phase 3 studies was the ACR20 response rate at 24 weeks. This endpoint is appropriate for evaluating the effect of treatment on the signs and symptoms of

PsA. The ACR response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA and PsA. The ACR criteria have been modified for PsA subjects by the addition of the DIP joints of the toes and the carpometacarpal joints (these joints are not included in the ACR response criteria for RA). A PsA patient with an ACR20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 76) and tender (maximum of 78) joint counts, as well as a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment of disease activity (PtGA), Physician's Global Assessment of disease activity (PhGA), Patient's Assessment of Pain score (on 10 cm VAS), Patient's assessment of physical function as measured by the HAQ-DI, and acute phase reactants (ESR or CRP). In both Phase 3 PsA trials, CRP was primarily used to calculate ACR response and ESR was only used if the CRP reading was missing. The ACR50 and ACR70 levels of response are calculated using the same criteria as the ACR20, but with a higher percentage improvement (50% and 70%, respectively) instead of 20%.

The secondary efficacy outcomes in the Phase 3 PsA studies (listed below in their sequential testing order; and all endpoints were evaluated at week 24) included:

- PASI75 response rate (in the subgroup of patients who had ≥3% skin involvement with psoriasis at baseline),
- PASI90 response rate (in the subgroup of patients who had ≥3% skin involvement with psoriasis at baseline),
- Least Square (LS) mean change from baseline in the Disease Activity Score (DAS) 28-CRP,
- LS mean change from baseline in the SF36-PCS score,
- LS mean change from baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI),
- ACR50 response rate,
- Joint/bone structural damage as measured by the van der Heijde-modified Total Sharp Score (vdH-mTSS) – only in Study F2306,
- Proportion of subjects with dactylitis (in the subset of patients with dactylitis at baseline), and
- Proportion of subjects with enthesitis (in the subset of patients with enthesitis at baseline).

There were also a large number of exploratory efficacy outcomes, but the important variables relating to this submission (only reported thus far for Study F2306) included:

- Proportion of patients achieving ACR20 response at week 52,
- Major Clinical Response (MCR) at week 52 – defined as subjects with a continuous 6 month period of maintaining an ACR70 response, and
- Change in joint structural damage from baseline to week 52, and between weeks 24 and 52 according to the vdH-mTSS and its sub-indices.

An understanding of the key secondary endpoints will help the interpretation of the results. The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (<10%) to six (90-100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease), and responses can be based on at least 50%, 75%, 90% and 100% improvement in

scores from baseline. The PASI 50 response is generally considered the minimal clinically important difference (MCID; Caitlin et al, 2004).

The 28 joint Disease Activity Score (DAS28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA and PsA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP and the PtGA. The final score is derived by a complex mathematical calculation of the individual elements. DAS28 has a scale from 0 to 10, and most scores range from around 2 to a maximum of 10. According to EULAR guidelines, a DAS28 score >5.1 indicates high disease activity, <3.2 indicates low disease activity, and clinical remission is indicated by a DAS28 score of <2.6.

The SF-36 (version 2) is a generic health assessment questionnaire intended to measure general health concepts not specific to any age, disease, or treatment group. This instrument has been validated in patients with PsA. It measures 8 health domains: Physical Functioning (PF; 10 questions), pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. It also can be subdivided into 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores. An improvement of >2.5 points in the PCS is defined as a clinically meaningful improvement in patients with active PsA.

The HAQ-DI is a validated method for measuring disability in inflammatory arthritis (range: 0-3 with higher score indicating more functional impairment). It assesses physical function by measuring the patient's ability to perform the following 8 activities (using 20 questions): dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity. The measure uses a scale ranging from zero (best) to three (worst). The MCID for the HAQ-DI score for patients with PsA has not been fully established but most clinicians consider a change in the HAQ-DI of -0.30 units to be the best validated cut-off threshold (Mease et al, 2011). However, other authors have suggested a much lower threshold of change (-0.13 units) as being acceptable (Kwok et al, 2010).

The van der Heijde - modified Total Sharp Score (vdH-mTSS) scoring method for PsA was used to assess structural joint damage, and its progression (van der Heijde et al, 2005). All enrolled subjects in Study F2306 were required to have X-rays taken of both hands and both feet (a single postero-anterior view of each hand, and a single dorso-plantar view of each foot) at baseline, weeks 24 and 52, or upon early withdrawal. Subjects who were classified as non-responders at week 16 on clinical criteria had their X-rays taken at this time point rather than week 24. X-ray images of both hands and feet were obtained using a slotting approach, digitized, and assessed by 2 central readers who were blinded to the treatment group, X-ray sequence and clinical status of the subject. In the scenario that adjudication was needed because of a discrepancy between the 2 reader values, a third consensus read was performed. The statistical analysis used the adjudicated score, if available or the average score from the 2 readers otherwise. The vdH-mTSS score is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0-528. The total vdH-mTSS score is the composite of the JSN score (range of 0-208; 26 sites on each side of the body scored from 0-4 for each site) and the ES (range of 0-320; 32 sites on each side of the body scored from 0-5 for each site). A higher score indicates more radiographic damage. Joints are divided into 10 anatomical regions. When 6 or more regions have an evaluable X-ray change from baseline, the overall change from baseline score is calculated with any missing segments imputed by the mean change over regions. However, if 5 or fewer regions have evaluable change, the overall change from baseline is reported as missing.

Enthesitis was assessed using the Leeds Enthesitis Index (LEI), which assesses 6 sites (e.g. proximal insertion of the Achilles tendons; left and right) in a dichotomous 0/1 score for tenderness. The index has a score range of 0-6. The presence and severity of dactylitis was assessed in both hands and feet (n=20 digits) using a dichotomous scoring system for each site

(with 0=not present and 1=present). The dactylitis score has a range from 0-20. There is no validated acceptance of what constitutes the MCID in enthesitis and dactylitis score.

Randomisation and blinding methods

At baseline, all eligible patients were randomised via interactive response technology (phone or web based) to 1 of the treatment arms. Patients in both Phase 3 studies were stratified at baseline according to whether or not they were anti-TNF experienced or naïve.

In Study F2306, PBO subjects who did not experience at least 20% improvement in tender and swollen joint counts by week 16 (i.e. met EE criteria) were required to switch over to active treatment with SEK - re-randomised 1:1 in a blinded fashion to either 75 mg or 150 mg given every 4 weeks by SC injection. Subjects on SEK who met the EE criteria continued to receive, in a blinded fashion, the same dose of SEK to which they were originally assigned. After 24 weeks, all subjects in the PBO group who had not entered EE at week 16 were to be re-randomised 1:1 to receive 75 mg or 150 mg of SEK every 4 weeks, stratified for past anti-TNF use (yes/no). Subjects who were receiving SEK from the start until week 24 continued to receive their randomised SEK treatment in a blinded manner until week 52.

In Study F2312, PBO subjects who did not experience at least 20% improvement in tender and swollen joint counts by week 16 (i.e. met EE criteria) were required to switch over to active treatment with SEK - re-randomised 1:1 in a blinded fashion to either 150 mg or 300 mg given every 4 weeks by SC injection. Subjects on SEK who met the EE criteria continued to receive, in a blinded fashion, the same dose of SEK to which they were originally assigned. After 24 weeks, all subjects in the PBO group who had not entered EE at week 16 were to be re-randomised 1:1 to receive 150 mg or 300 mg of SEK every 4 weeks, stratified for past anti-TNF use (yes/no). Subjects who were receiving SEK from the start until week 24 continued to receive their randomised SEK treatment in a blinded manner until week 52. To maintain blinding in Study F2312, 3 matching injections (supplied in prefilled syringes) were given SC to all subjects at each visit. Three simultaneous injections were necessary as SEK was provided in 2 syringe sizes (0.5 mL containing SEK 75 mg and 1.0 mL containing SEK 150 mg). When therapy with SEK 300 mg was required, this was administered as 2 x 1.0 mL injections. Placebo injections were supplied in 0.5 mL and 1.0 mL syringes to match the presentation of SEK injections.

In both Phase 3 studies, each subject received a randomisation number, which was linked to a specified unique medication sequence communicated to an unblinded site pharmacist, who prepared the study treatment. Patients, investigator staff (with the exception of the site pharmacist), persons performing the assessments and data analysts remained blinded to the identity of study treatment from the time of subject randomisation until database lock (i.e. when all enrolling patients had completed their week 52 assessments).

In Study F2306, a central reading process performed X-ray interpretations, with personnel blinded to study treatment, X-ray sequence and clinical status.

Analysis populations

In both Phase 3 studies, all efficacy analyses for primary and secondary efficacy endpoints were conducted using the Full Analysis Set (FAS). The FAS consisted of all subjects (including both anti-TNF experienced and naïve) who were randomised and to who study treatment had been assigned. Subjects who were randomised in error and did not receive any dose of study drug (SEK or PBO) were excluded from FAS and managed as screen failures. However, any subjects who were randomised in error but did receive at least 1 dose of study drug (SEK or PBO) were to be included in the treatment group to which they were randomised. For the analyses using the FAS, subjects were included in the treatment group to which they were randomised, irrespective of the treatment actually received. No analysis using the per-protocol population was provided for either Phase 3 trial.

Sample size

Study F2306

The sample size calculations for Study F2306 were based on the results of the 2 Phase 3 studies (PSUMMIT I [McInnes et al, 2013] and PSUMMIT II [Ritchlin et al, 2013]), which evaluated the efficacy of ustekinumab in adult patients with active PsA. A placebo response (ACR20 response) of 25% after 24 weeks was reported for the anti-TNF naïve population in PSUMMIT I and 15% was stated for the anti-TNF-IR responder population in PSUMMIT II. Based on the weighted average, the overall PBO response rate was expected to be 22% in Study F2306. The ACR20 response rate at 24 weeks with SEK was estimated to be 55% in the anti-TNF naïve population and 35% in the anti-TNF-IR group. Based on the weighted average, the overall SEK response rate was expected to be 49% in Study F2306. For the primary endpoint of ACR20 response at 24 weeks, 200 patients per treatment group would yield 99% power to detect a treatment related difference with SEK versus PBO in Study F2306 (using Fisher's exact test). A 5% 2-sided type I error rate was used to control for type I error. Because 2 doses of SEK were examined in Study F2306, the type I error was split to 2.5% 2-sided for each SEK dose comparison versus PBO. As it was planned that 30% of recruited patients would be anti-TNF-IR, it was estimated that Study F2306 would enrol 180 anti-TNF-IR subjects and 420 anti-TNF naïve patients. In addition, a screen failure rate of ~30% was estimated. Hence, Study F2306 aimed to screen 850 subjects with the expectation of randomising 600 subjects. The trial plan also estimated a post-randomisation rate of 20% by year 1 and 25% at 2 years.

The study protocol also calculated the statistical power for each of the secondary efficacy variables. Of note, is the power calculation for the structural (X-ray) endpoint. Historical data with adalimumab in adult patients with active PsA showed a SD of 1.2 on anti-TNF therapy and 2.4 on PBO at week 26, and a between-treatment difference of 0.6 for the TNF naïve population (Mease et al, 2005). The protocol assumes half the between-treatment difference for anti-TNF-IR subjects, resulting in the estimated overall F2306 population showing a between-treatment difference for SEK versus PBO of 0.51. Using the above assumptions, there was 80% power for Study F2306 to show a statistically significant difference between SEK (pooled 400 patients) and PBO (200 subjects).

Study F2312

Study F2312 used the same published data and assumptions as Study F2306 to estimate the required sample size. A 5% 2-sided type I error rate was used to control for type I error. However, because 3 doses of SEK were examined in Study F2312, the type I error was split to 1.7% 2-sided for each SEK dose comparison versus PBO. Based on the weighted average of the above response rates, the overall SEK response rate was expected to be 47% in Study F2312 and the PBO response rate was estimated to be 21%. For the primary endpoint of ACR20 response at 24 weeks, 100 patients per treatment group would yield 92% power to detect a treatment related difference of 26% with SEK versus PBO in Study F2312 (using Fisher's exact test). The trial planned to recruit 40% of patients as being anti-TNF-IR, so it was estimated that Study F2312 would enrol 160 anti-TNF-IR subjects and 240 anti-TNF naïve patients.

The study protocol also calculated the statistical power for each of the secondary clinical efficacy variables. The skin outcomes and mean changes from baseline in DAS28, HAQ-DI and SF36-PCS scores were all estimated to have >90% statistical power. The treatment related difference in ACR50 response had approximately 78% power, while the presence of dactylitis and enthesitis at 24 weeks had about 60-63% power to detect a treatment related difference between SEK and PBO.

Statistical methods

In both Phase 3 studies, a sequentially rejective testing strategy was used to evaluate the study hypotheses for the primary and secondary efficacy variables to protect the family-wise type I error rate at 5%. The statistical hypothesis for the primary efficacy outcome (ACR20 response

rate at week 24) being tested was that there was no difference between any of the SEK treatment regimens versus PBO.

For the secondary efficacy endpoints, a pre-defined statistical testing hierarchy was outlined:

- SEK (any dose arm) was no different to PBO for the PASI75 response rate at week 24,
- SEK (any dose arm) was no different to PBO for the PASI90 response rate at week 24,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in DAS28-CRP at week 24,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in SF36-PCS at week 24,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in HAQ-DI at week 24,
- SEK (any dose arm) was no different to PBO for the ACR50 response rate at week 24,
- SEK (pooled results) as well as each individual SEK dose regimen were no different to PBO regarding change in vdH-mTSS at week 24 – only in Study F2306,
- SEK (pooled results) were no different to PBO regarding presence of dactylitis at week 24, &
- SEK (pooled results) were no different to PBO regarding presence of enthesitis at week 24.

The primary efficacy endpoint of ACR20 response at week 24 was analysed using a logistic regression model fitted with treatment and prior anti-TNF use (yes/no) as factors, and subject weight as a covariate. Odds Ratios (OR) were computed for comparisons between SEK regimens versus PBO utilising the logistic regression model. For patients meeting the EE criteria at week 16, their ACR20 response was set to non-response at week 24 (in order to minimise bias). Patients who discontinued from the trial (for any reason) prior to week 52 were considered non-responders. Similarly, subjects who did not have sufficient available data to compute the ACR response at baseline or any time thereafter were also classified as non-responders. Sensitivity analysis using the observed data was also performed to support the integrity of the primary analysis. Other binary variables such as the rate of ACR50 and PASI response were managed in the same manner as the ACR20 analysis.

Continuous endpoints such as the change from baseline in DAS28-CRP, HAQ-DI and SF-36 scores were evaluated using a mixed-effects repeated measures model with treatment regimen, prior anti-TNF use and visit as factors. An unstructured covariance structure was assumed for this model.

The primary radiographic analysis used linear extrapolation of scores from the last 2 radiographs taken at or before week 24 for the handling of missing data. Treatment related differences were estimated based on a non-parametric Analysis of Covariance (ANCOVA) model. For subjects who met the EE criteria at week 16, their X-rays were acquired at week 16 and carried forward to the week 24 assessment. A sensitivity analysis using the removal of outliers (values +/- 3 SD outside observations for the vdH-mTSS) was performed for the change from baseline in vdH-mTSS using ANCOVA with linear extrapolation. Another sensitivity analysis using the X-ray completer cohort, defined as those subjects with X-ray measures at baseline and weeks 24 and 52, was also performed. In addition, to assess the model for the treatment effects with SEK, the ANCOVA model included an assessment of treatment response by prior anti-TNF exposure and concomitant MTX.

Participant flow

Study F2306

In Study F2306, a total of 817 subjects were screened for inclusion, of which 606 (202 in each of the 3 treatment groups) were randomised and included in the FAS. The most frequent reason

for discontinuation prior to randomisation (n=211 subjects) was screen failure (23.4% in total; 191/817) followed by subjects or guardian withdrawal of consent (2.0% in total; 16/817). Screen failure was due to a combination of not meeting inclusion criteria (n=112; mainly due to positive rheumatoid factor or anti-CCP antibodies [n=73]) and those with 1 or more exclusion criterion (n=99; mainly due to history of chronic or recurrent infection, including latent TB [n=36] or abnormal liver function tests at baseline [n=13]).

A total of 95.2% (577/606) of subjects continued until the week 16 assessment visit (i.e. true PBO controlled period) at a similar frequency in each of the 3 treatment groups: 96.0% (194/202) in the SEK 75 mg group, 97.0% (196/202) in the SEK 150 mg arm and 92.6% (187/202) in the PBO group. Expectedly, the proportion of subjects who met the criteria for EE at week 16 was substantially higher in the PBO group (65.8%; 123/202 – 61 received to SEK 75 mg and 60 received to SEK 150 mg injections [note: 1 re-randomised patient in each SEK group did not actually receive any SEK) compared to the SEK treatment groups (23.7% [46/202] in the 75 mg group and 26.0% [51/202] in the 150 mg dose arm).

Overall, 85.0% (515/606) of subjects completed 52 weeks of treatment follow-up in Study F2306: 79.7% (161/202) in the PBO group, 86.1% (174/202) in the SEK 75 mg arm and 89.1% (180/202) in the SEK 150 mg group. For the 91 subjects who had discontinued by week 52, the most common reasons were lack of efficacy (26 patients), withdrawal of consent (23 subjects) and adverse events (20 patients). All 3 reasons for premature discontinuation occurred at a higher frequency in the PBO group: 6.4% (13/202) for lack of efficacy, 5.9% (12/202) for consent withdrawal and 4.5% (9/202) for adverse events compared to the following incidences in the SEK 75 mg and 150 mg treatment arms, respectively: 3.0% (6/202) and 3.5% (7/202) for lack of efficacy; 3.0% (6/202) and 2.5% (5/202) for consent withdrawal; and 3.0% (6/202) and 2.5% (5/202) for adverse events.

Of the 202 patients initially randomised into the PBO group, 187 were re-randomised at same stage in the study, but 4 of those subjects withdrew from the trial prior to receiving any dose of SEK. A total of 123 PBO patients met the criteria for EE at week 16, 62 of whom were re-randomised to SEK 75 mg injections and 61 patients were re-randomised to SEK 150 mg injections. Of the 60 patients who continued on PBO until 24 weeks, 28 were re-randomised to SEK 75 mg injections and 32 were re-randomised to SEK 150 mg SC injections every 4 weeks. Of the 41 (20.3% of 202) PBO patients who discontinued prior to week 52, 19 (9.8%) discontinued while receiving PBO injections, 8 (4.0%) ceased involvement after switching to SEK 75 mg injections and 14 (6.9%) discontinued after changing to SEK 150 mg therapy.

Study F2312

In Study F2312, a total of 469 subjects were screened for inclusion, of which 397 (84.6%) were randomised and included in the FAS (100 subjects each in the SEK 150 mg and 300 mg groups, 99 patients in the SEK 75 mg arm and 98 subjects in the PBO group). The most frequent reason for discontinuation prior to randomisation (n=72 subjects) was screen failure (13.42% in total; 62/469) followed by subjects or guardian withdrawal of consent (1.9% in total; 9/469). Screen failure was due to a combination of not meeting inclusion criteria (n=23; mainly due to positive rheumatoid factor or anti-CCP antibodies [n=20]) and those with 1 or more exclusion criterion (n=41; mainly due to history of chronic or recurrent infection, including latent TB [n=10] or abnormal liver function tests at baseline [n=8]).

A total of 95.5% (379/397) of subjects continued until the week 16 assessment visit (i.e. true PBO controlled period) at a similar frequency in each of the 3 SEK treatment groups (94.9% [94/99] in the SEK 75 mg group, 98.0% [98/100] in the SEK 150 mg arm and 97.0% [97/100] in the SEK 300 mg group) but at a slightly lower rate in the PBO arm (91.8%; 90/98). Expectedly, the proportion of subjects who met the criteria for EE at week 16 was substantially higher in the PBO group (61.1%; 55/98 – 27 were re-randomised to receive SEK 150 mg therapy and 28 were re-randomised to receive SEK 300 mg injections) compared to the SEK treatment groups

(51.1% [48/99] in the 75 mg group, 33.0% [33/100] in the 150 mg dose arm and 25.0% [25/100] in the 300 mg dose group).

Overall, 94.0% (373/397) of subjects completed 24 weeks of treatment follow-up in Study F2312: 89.8% (88/98) in the PBO group, 93.9% (93/99) in the SEK 75 mg arm, 95.0% (95/100) in the SEK 150 mg group and 97.0% (97/100) in the SEK 300 mg arm. For the 24 subjects who had discontinued by week 24, the 2 most common reasons were adverse events (9 patients) and lack of efficacy (8 subjects). Both reasons for premature discontinuation occurred at a similar or higher frequency in the PBO group: 4.1% (4/98) for adverse events and 3.1% (3/98) for lack of efficacy compared to the following incidences in the SEK 75 mg, 150 mg and 300 mg treatment arms, respectively: 3.0% (3/99), 0 and 2.0% (2/100) for adverse events; and 2.0% (2/99), 3.0% (3/100) and 0 for lack of efficacy. The interim report for Study F2312 provided in this submission had very limited numbers of patients with reported efficacy data (n=7 subjects in total) at week 52, although the full safety data for patients up to week 52 was included.

Of the 98 patients initially randomised into the PBO group, 88 were re-randomised at same stage in the study, but 4 of those subjects withdrew from the trial prior to receiving any dose of SEK. A total of 55 PBO patients met the criteria for EE at week 16, 27 of whom were re-randomised to SEK 150 mg injections and 28 patients were re-randomised to SEK 300 mg injections. Of the 33 patients who continued on PBO until 24 weeks, 16 were re-randomised to SEK 150 mg injections and 17 were re-randomised to SEK 300 mg SC injections every 4 weeks.

Major protocol violations/deviations

Study F2306

No patient was excluded from the FAS because of protocol deviations. However, a total of 166 subjects (27.4% of 606) had documented protocol deviations up to week 24. These occurred at a similar incidence in each of the 3 treatment groups: 28.7% (58/202) in the SEK 75 mg group, 23.8% (48/202) in the SEK 150 mg arm and 29.7% (60/202) in the PBO group. It is unclear whether or not these protocol deviations had the potential to impact upon efficacy assessments as the sponsor has not presented the efficacy data using a per protocol population analysis. The 4 most common reasons for protocol deviations included “key procedures not performed as per protocol” (12.9% in the SEK 75 mg group, 8.9% in the SEK 150 mg arm and 6.9% in the PBO group), “GCP related deviations” (12.4% in the SEK 75 mg group, 6.4% in the SEK 150 mg arm and 9.4% in the PBO group), selection criteria not met (6.9% in the SEK 75 mg group, 3.5% in the SEK 150 mg arm and 7.9% in the PBO group) and use of prohibited concomitant medication (4.5% in the SEK 75 mg group, 4.5% in the SEK 150 mg arm and 5.9% in the PBO group). The sponsor should provide further detail on the specific nature of the protocol deviations and how they may have potentially impacted upon the efficacy results.

At 52 weeks, 34.7% (70/202) of subjects in the SEK 75 mg group, 31.2% (63/202) of patients in the SEK 150 mg arm and 34.2% (69/202) of subjects in the PBO group had at least 1 protocol violation recorded. The most common types of protocol violations recorded during the entire treatment period (across all treatment groups) were similar to that observed at week 24.

Study F2312

No patient was excluded from the FAS because of protocol deviations. Up to week 24, a total of 64 subjects (16.0% of 397) had documented protocol deviations. These occurred at a lower rate in the SEK 75 mg group (13.1%; 13/99) but at a higher and similar incidence in each of other 3 treatment groups (15.0% [15/100] in the SEK 150 mg group, 18.0% [18/100] in the SEK 300 mg arm and 18.4% [18/98] in the PBO group). It is unclear whether or not these protocol deviations had the potential to impact upon efficacy assessments as the sponsor has not presented the efficacy data using a per protocol population analysis. The 3 most common reasons for protocol deviations were “GCP related deviations” (6.1% in the SEK 75 mg group, 3.0% in the SEK 150 mg arm, 4.0% in the SEK 300 mg group and 8.2% in the PBO arm), selection criteria not met (1.0% in the SEK 75 mg group, 4.0% in the SEK 150 mg arm, 4.0% in

the SEK 300 mg group and 6.1% in the PBO arm) and use of prohibited concomitant medication (3.0% in the SEK 75 mg group, 6.0% in the SEK 150 mg arm, 4.0% in the SEK 300 mg group and 2.0% in the PBO arm). The sponsor should provide further detail on the specific nature of the protocol deviations and how they may have potentially impacted upon the efficacy results.

The percentages of subjects reporting at least 1 protocol deviation during the entire treatment period (i.e. up to week 52) was 19.2% in the SEK 75 mg group, 21.0% in the SEK 150 mg arm, 23.0% in the SEK 300 mg group and 24.5% in the PBO arm. The most common types of protocol violations recorded during the entire treatment period (across all treatment groups) were similar to that observed at week 24.

Baseline data

Study F2306

The 3 treatment groups in this trial were well matched at baseline for demographic characteristics. The majority of subjects enrolled in this trial were <65 years of age (89.1% [180/202] in each SEK treatment group and 95.0% [192/202] in the PBO arm) with a mean age of 49 years (range: 20-77 years). Just over half (52.5%; 330/606) of all patients were female and over three-quarters of all subjects (79.4%; 481/606) were Caucasian. The mean BMI was slightly higher in the SEK treatment groups at 29.86-30.05 kg/m^2 compared to subjects in the PBO arm who had a mean BMI of 28.67 kg/m^2. Almost 20% (19.1%; 116/606) of subjects were current smokers.

The 3 treatment groups were similar with respect to baseline PsA features. The mean duration of PsA was 7.44 years (median 4.38 years, range: 0.02-48.3 years) for subjects in the PBO group, 7.83 years (median 5.10 years, range: 0.04-49.3 years) for patients in the SEK 75 mg arm and 8.34 years (median 5.34 years, range: 0.04-45.7 years) for patients in the SEK 150 mg group. More than half of all subjects had enthesitis (61.4%; 372/606) and/or dactylitis (53.5%; 324/606) at baseline. Regarding skin psoriasis characteristics, just over half of all subjects (53.6%; 325/606) had at least 3% BSA involvement with skin psoriasis at baseline with equal numbers of affected patients in each of the 3 treatment groups (n=108-109). In the subset of patients with ≥3% BSA psoriasis, the mean baseline PASI score was lower at 10.67 in the SEK 75 mg group compared with 15.62 in the SEK 150 mg arm and 15.10 in the PBO group. In addition, a higher proportion of subjects in the PBO group (57.8%; 63/109) had a baseline PASI score >10 versus 53.7% (58/108) in the SEK 150 mg arm and 40.7% (44/108) in the SEK 75 mg group.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for both SEK treatment groups at 23.4-23.8 (maximum of 78) and 12.5-12.7 (maximum of 76), respectively. However, the PBO group had a higher mean number of tender (25.1) and swollen joints (14.9) at baseline, but the median affected values were similar between all 3 treatment groups (19.0-20.5 for tender joints and 9.0-10.0 for swollen joints). The mean HAQ-DI score was slightly lower in the PBO group at 1.19 compared with 1.25 in the SEK 75 mg arm and 1.23 in the SEK 150 mg treatment group. The mean PtGA and PhGA were similar in the 3 treatment groups at 55.2-56.1 mm and 54.3-56.7 mm, respectively. The mean baseline DAS28-CRP scores were similar in the PBO and SEK 75 mg treatment groups (4.93 and 4.89, respectively) but slightly lower in the SEK 150 mg arm at 4.78.

The majority of subjects (60.7%; 368/606 [n=121-125 subjects in each of the 3 treatment groups] were taking MTX at baseline at a median weekly dose of 15 mg (mean weekly dose ranging from 14.4-15.3 mg). Regarding prior conventional DMARD exposure, 69.6% (281/606) had a history of MTX use, 11.9% (48/606) had previously tried sulfasalazine and 12.9% (52/606) had a history of leflunomide therapy. Consistent with the protocol, more than two thirds of all subjects (70.5%; 427/606 [n=142-143 subjects in each of the 3 treatment groups]) were naïve to anti-TNF drugs. In those who had received prior anti-TNF therapy, most had experience with only 1 agent (18.2%; 110/606). A smaller proportion of subjects (11.4%;

69/606) had experienced 2 or 3 previous anti-TNF therapies. The incidence and pattern of past anti-TNF exposure was similar across the 3 treatment groups. A small but similar proportion of subjects in each treatment group were using systemic CS at baseline (15.7%; 95/606) but regular NSAID use was common (72.4%; 439/606). Less than 10% of all subjects (9.9%; 60/606) were taking medicines for gastro-oesophageal reflux and/or peptic ulcer prevention. Past history of hypertension was recorded at a slightly lower incidence in SEK treatment groups (38.6-40.6%) than the PBO arm (41.6%). A history of hyperlipidaemia was recorded at a higher incidence in the SEK 150 mg and PBO treatment groups (25.2-27.2%) than the SEK 75 mg arm (20.8%).

Study F2312

The 4 treatment groups were reasonably well matched at baseline for demographic characteristics. The majority of subjects enrolled in this trial were <65 years of age (93.9% [93/99] in the SEK 75 mg treatment group, 94.0% [94/100] in the SEK 150 mg arm, 90.0% [90/100] in the SEK 300 mg group and 88.8% [87/98] in the PBO arm) with a mean age of 46.5-49.9 years (range: 20-77 years). Over half of the patients in the SEK 75 mg (52.5%; 52/99) and PBO groups (60.2%; 59/98) were female but the converse was true for the SEK 150 mg group (55% male; 55/100). In the SEK 300 mg group, the relative gender distribution was similar (49 females and 51 males). More than 90% of participants in each treatment group were Caucasian. The mean BMI was similar in each of the 4 treatment groups at 29.4-31.2 kg/m^2. Almost 20% (19.4%; 77/397) of all subjects were current smokers at baseline.

The 4 treatment groups were also similar with respect to baseline PsA features. The mean duration of PsA was 7.32 years (median 4.95 years) for subjects in the PBO group, 6.48 years (median 3.93 years) for patients in the SEK 75 mg arm, 6.51 years (median 4.30 years) for patients in the SEK 150 mg group and 7.38 years (median 4.71 years) for patients in the SEK 300 mg arm. More than half of all subjects had enthesitis (63.7%; 253/397) at baseline but only a third had dactylitis (34.8%; 138/397) at baseline. Regarding skin psoriasis characteristics, just less than half of all subjects (48.4%; 192/325) had at least 3% BSA involvement with skin psoriasis at baseline with varying numbers of affected patients in each of the 4 treatment groups. In the subset of patients with ≥3% BSA psoriasis, the mean baseline PASI score was higher at 16.16 in the SEK 150 mg group (n=58 subjects) compared with 12.11 in the SEK 75 mg arm (n=50), 11.94 in the SEK 300 mg group (n=41) and 11.55 in the PBO arm (n=43). In addition, a higher proportion of subjects in the SEK 150 mg group (56.9%; 33/58) had a baseline PASI score >10 versus 44.0% (22/50) in the SEK 75 mg arm, 48.8% (20/41) in the SEK 300 mg group and 46.5% (20/43) in the PBO arm.

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were lower in the SEK 75 mg and 300 mg treatment groups at 20.2-22.2 (maximum of 78) and 10.8-11.2 (maximum of 76), respectively. However, the PBO and SEK 150 mg groups had a higher mean number of tender (23.4-24.1) and swollen joints (11.9-12.1) at baseline, but the median affected values were similar between all 4 treatment groups (17.0-18.0 for tender joints and 8.0-9.0 for swollen joints). The mean HAQ-DI score was slightly lower in the PBO (1.17) and SEK 75 mg groups (1.16) compared with 1.22 in the SEK 150 mg arm and 1.28 in the SEK 300 mg treatment group. The mean PtGA and PhGA were similar in the 4 treatment groups at 57.6-62.0 mm and 55.0-59.0 mm, respectively. The mean baseline DAS28-ESR scores were similar in the PBO and SEK 300 mg treatment groups (5.18 and 5.19, respectively), but slightly lower in the SEK 75 mg arm at 5.13, and somewhat higher in the SEK 150 mg group at 5.27.

In each of the SEK treatment groups, a minority of subjects (45.2%; 135/299 [n=44-47 subjects in each of the 3 SEK treatment groups] were taking MTX at baseline at a mean weekly dose of 16.1-18.0 mg. Just over half of enrolled subjects in the PBO group (51.0%; 50/98) were taking MTX at randomisation at a mean weekly dose of 17.6 mg. Regarding prior conventional DMARD exposure in the pooled SEK treatment cohort, 59.2% (177/299) had a history of MTX use, 12.7% (38/299) had previously tried sulfasalazine and 10.7% (32/299) had a history of

leflunomide therapy. About two thirds of all subjects (65.0%; 258/397 [n=63-67 subjects in each of the 4 treatment groups]) were naïve to anti-TNF drugs. In those who had received prior anti-TNF therapy, most had experience with only 1 agent (19.9%; 79/397). A smaller proportion of subjects (15.1%; 60/397) had experienced 2 or 3 previous anti-TNF therapies. The incidence and pattern of past anti-TNF exposure was similar across the 4 treatment groups. A low and similar proportion of subjects in each treatment group were using systemic CS at baseline (20.4%; 81/397) but regular NSAID use was common (79.6%; 316/397).

A history of hypertension was recorded in 40.4-43.0% of subjects in each of the 4 treatment groups, hyperlipidaemia was recorded in 20.2-25.5% of subjects and uncomplicated diabetes was recorded in 9.0-13.1% of participants in each of the 4 treatment groups.

Results for the primary efficacy outcome

Study F2306

This trial achieved the primary efficacy endpoint with both doses of SEK being statistically superior to PBO in reducing the symptoms and signs of active PsA at week 24 (using Non-Responder Imputation [NRI] for the FAS cohort). The rate of ACR20 response at week 24 was 50.5% (102/202) in the SEK 75 mg group and 50.0% (101/202) in the SEK 150 mg arm versus 17.3% (35/202) in the PBO group ($p<0.001$ for both SEK comparisons versus PBO). Similar efficacy response rates were observed in the SEK 75 mg and 150 mg groups at week 24 due to the effect of high drug exposure achieved by the IV loading dose (3 x 10 mg/kg infusions in the first 4 weeks) and the long half life of the therapy. As a consequence, drug exposure in both SEK treatment groups was similar over the first 24 weeks of treatment follow-up and no significant difference in treatment response was observed in the relatively short time frame.

The Odds Ratio (OR) of achieving an ACR20 response at week 24 for SEK 75 mg versus PBO was 5.53 (95% CI 3.46, 8.85; $p<0.001$). The OR of achieving an ACR20 response at week 24 for SEK 150 mg versus PBO was 5.39 (95% CI 3.37, 8.62; $p<0.001$).

As a supporting analysis, the sponsor has provided the rates of ACR20 response at weeks 16 and 24 using the observed data. This demonstrates a robust treatment effect with both doses of SEK on the symptoms and signs of active PsA. At week 16 using observed data, the rate of ACR20 response was 56.1% (106/189) in the SEK 75 mg group, 60.2% (115/191) in the SEK 150 mg arm and 23.5% (43/183) in the PBO group. At week 24 using observed data, the rate of ACR20 response was 61.5% (115/187) in the SEK 75 mg group, 61.2% (115/188) in the SEK 150 mg arm and 46.6% (81/174) in the PBO group.

The rate of ACR20 response (using NRI in the FAS cohort) was higher for both doses of SEK compared to PBO irrespective of the prior anti-TNF status of the subject. However, anti-TNF naïve subjects had higher ACR20 response rates (55.6% [79/142] for SEK 75 mg and 54.5% [78/143] for SEK 150 mg) compared to anti-TNF-IR subjects (38.3% [23/60] for SEK 75 mg and 39.0% [23/59] for SEK 150 mg) at week 24. The PBO group ACR20 response rates at 24 weeks were 17.5% (25/143) in the anti-TNF naive subset and 16.9% (10/59) in the anti-TNF-IR cohort. However, the concurrent use of MTX did not appear to impact upon the ACR20 response rate at 24 weeks. In the patients taking concurrent MTX in Study F2306, the ACR20 response rate at 24 weeks was 49.2% (60/122) in the SEK 75 mg group, 52.1% (63/121) in the SEK 150 mg arm and 19.2% (24/125) in the PBO group. In the subset of patients not taking concomitant MTX in Study F2306, the ACR20 response rate at 24 weeks was 52.5% (42/80) in the SEK 75 mg group, 46.9% (38/81) in the SEK 150 mg arm and 14.3% (11/77) in the PBO group.

Study F2312

All 3 doses of SEK were statistically superior to PBO in demonstrating a higher rate of ACR20 response at 24 weeks (using NRI for the FAS cohort). The rate of ACR20 response at week 24 was 29.3% (29/99) in the SEK 75 mg group ($p=0.0200$), 51.0% (51/100) in the SEK 150 mg arm ($p<0.0001$) and 54.0% (54/100) in the SEK 300 mg arm ($p<0.0001$) versus 15.3% (15/98) in

the PBO group. Thus, the primary endpoint of the trial was met using the pre-defined statistical hierarchy. However, the magnitude of the treatment effect with SEK versus PBO was similar with the 2 higher doses of SEK (150 mg and 300 mg) but considerably lower (i.e. <15% difference in response rates) for SEK 75 mg injection therapy compared to PBO.

The OR of achieving an ACR20 response at week 24 for SEK 75 mg versus PBO was 2.32 (95% CI 1.14, 4.73; p=0.02). The OR of achieving an ACR20 response at week 24 for SEK 150 mg versus PBO was 6.52 (95% CI 3.25, 13.08; p<0.001) and for SEK 300 mg treatment versus PBO was 6.81 (95% CI 3.42, 13.56; p<0.001).

As a supporting analysis, the sponsor has provided the rates of ACR20 response at weeks 16 and 24 using the observed data. This demonstrates a robust treatment effect with all 3 doses of SEK on the rate of ACR20 response. At week 16 using observed data, the rate of ACR20 response was 35.5% (33/93) in the SEK 75 mg group, 60.0% (60/100) in the SEK 150 mg arm, 60.0% (57/95) in the SEK 300 mg group compared with 20.9% (18/86) in the PBO arm. At week 24 using observed data, the rate of ACR20 response was 49.4% (44/89) in the SEK 75 mg group, 62.1% (59/95) in the SEK 150 mg arm, 70.2% (66/94) in the SEK 300 mg group and 40.2% (35/87) in the PBO arm.

Similar to the observations in Study F2306, the rate of ACR20 response in Study F2312 (using NRI in the FAS cohort) was numerically greater for the 2 higher doses of SEK compared to PBO irrespective of the prior anti-TNF status of the subject. However, in the anti-TNF experienced subset, a statistically higher rate of ACR20 response was only demonstrated with SEK 300 mg therapy (45.5%; 15/33) compared to PBO (14.3% [5/35]; p=0.0077). Treatment with SEK 75 mg (14.7%; 5/34) or SEK 150 mg injections (29.7%; 11/37) was not statistically better than PBO in the anti-TNF-IR cohort (p=0.9639 and p=0.1216, respectively). In the anti-TNF naïve subset, the 24 week ACR20 responder rate was statistically better in all 3 SEK dose groups versus PBO (36.9% [24/65] for SEK 75 mg [p=0.0075], 63.5% [40/63] for SEK 150 mg [p<0.0001] and 58.2% [39/67] for SEK 300 mg [p<0.0001] versus 15.9% [10/63] in the PBO group.

The concurrent use of MTX did not appear to impact upon the ACR20 response rate at 24 weeks in subjects receiving SEK 150 mg and 300 mg injections. However, in those who were given SEK 75 mg injections, the ACR20 response was numerically higher when SEK was combined with MTX. In the patients taking concurrent MTX in Study F2312, the ACR20 response rate at 24 weeks was 44.7% (21/47) in the SEK 75 mg group, 47.7% (21/44) in the SEK 150 mg arm, 54.5% (24/44) in the SEK 300 mg group and 20.0% (10/50) in the PBO arm. In the subset of patients not taking concomitant MTX in Study F2312, the ACR20 response rate at 24 weeks was 15.4% (8/52) in the SEK 75 mg group, 53.6% (30/56) in the SEK 150 mg arm, 53.6% (30/56) in the SEK 300 mg group and 10.4% (5/48) in the PBO arm.

Although randomisation was not stratified by body weight, ACR20 responses at 24 weeks were additionally analysed by weight group (<100 kg versus ≥100 kg). In the subgroup of patients weighing ≥100 kg, a statistically higher rate of ACR20 response was only demonstrated with SEK 300 mg therapy (61.1%; 11/18) compared to PBO (10.0% [2/20]; p=0.0029). Treatment with SEK 75 mg (28.0%; 7/25) or SEK 150 mg injections (33.3%; 11/33) was not statistically better than PBO in the patient cohort weighing ≥100 kg (p=0.1725 and p=0.0795, respectively). In the patient subset weighing <100 kg, the 24 week ACR20 responder rate was statistically better in the 2 higher SEK dose groups versus PBO (59.7% [40/67] for SEK 150 mg [p<0.0001] and 52.4% [43/82] for SEK 300 mg [p<0.0001] versus 16.7% [13/78] in the PBO group. The ACR20 response in group of patients weighing <100 kg who received SEK 75 mg injection was 29.7% (22/74), which was not statistically different to PBO (p=0.0637).

Results for other efficacy outcomes

Study F2306

In addition to achieving the primary efficacy outcome, Study F2306 demonstrated that SEK 75 mg and 150 mg were superior to PBO at week 24 for all secondary efficacy endpoints in the statistical testing hierarchy – refer to Table 11.

Table 11: Results for Secondary Efficacy Endpoints in Study F2306 as per Hierarchical Testing.

Endpoint	Secukinumab 10 mg/kg - 75 mg (N=202)	Secukinumab 10 mg/kg - 150 mg (N =202)	Pooled Secukinumab (N =404)	Placebo (N =202)
PASI 75	64.8% p < 0.0001	61.1% p < 0.0001	--	8.3%
PASI 90	49.1% p < 0.0001	45.4% p < 0.0001	--	3.7%
DAS28-CRP	-1.67 p < 0.0001	-1.62 p <0.0001	--	-0.77
SF-36 PCS	5.41 p < 0.0001	5.91 p < 0.0001	--	1.82
HAQ-DI©	-0.41 p < 0.0001	-0.40 p < 0.0001	--	-0.17
ACR 50	30.7% p < 0.0001	34.7% p < 0.0001	--	7.4%
van der Heijde modified total Sharp score**	0.02 p = 0.0132	0.13 p = 0.0212	0.08 p = 0.0113	0.57
Presence of Dactylitis**	43.3% p < 0.0001	51.9% p < 0.0001	47.6% p < 0.0001	84.5%
Presence of Enthesitis**	51.2% p < 0.0001	54.0% p < 0.0001	52.5% p < 0.0001	87.2%

**hierarchy order is first pooled van der Heijde modified total Sharp score, followed by pooled dactylitis and enthesitis scores, lastly van der Heijde modified total Sharp score for individual doses. Individual doses for dactylitis and enthesitis are not in the hierarchy

Skin outcomes

Both doses of SEK were superior to PBO for the rate of PASI75 and PASI90 response at week 24 in the FAS (p<0.0001 for all pair-wise treatment comparisons between either dose of SEK and PBO).

At week 24, the PASI75 response rate was 64.8% (70/108) for the SEK 75 mg group and 61.1% (66/108) for the SEK 150 mg arm compared with 8.3% (9/109) for the PBO group. The PASI90 response rate at 24 weeks was 49.1% (53/108) for the SEK 75 mg group and 45.4% (49/108) for the SEK 150 mg arm compared with 3.7% (4/109) for the PBO group.

Disease activity

Using the FAS cohort, both doses of SEK were superior to PBO for the LS mean change from baseline to week 24 in the DAS28-CRP score (p<0.0001 for both SEK treatment comparisons with PBO). At week 24, the LS mean change from baseline in the DAS28-CRP score was -1.67 (n=186; baseline mean score=4.89) for the SEK 75 mg group and -1.62 (n=188; baseline mean score=4.78) for the SEK 150 mg arm compared with -0.77 (n=58; baseline mean score=4.93) for the PBO group.

Quality of life

At 24 weeks, statistically greater improvements in the LS mean change from baseline in the SF36-PCS score were reported for both doses of SEK (5.41 for the 75 mg dose group [n=191]

and 5.91 for the 150 mg arm [n=190] compared to PBO (1.82 [n=63]; p<0.0001 for both doses of SEK versus PBO). However, I was unable to locate the mean baseline SF36-PCS scores in the submission to interpret the relative change in this variable from baseline.

Physical functioning

Improvements in physical function and disability as measured by the LS mean change from baseline to week 24 in HAQ-DI score were -0.41 for the SEK 75 mg group (n=187; baseline mean score=1.25) and -0.40 for the SEK 150 mg arm (n=189; baseline mean score=1.23) compared to -0.17 for the PBO group (n=58; baseline mean score=1.19). Both doses of SEK were statistically superior to PBO for this outcome (p<0.0001).

ACR50 response

Both doses of SEK were superior to PBO for the rate of ACR50 response at week 24 in the FAS (p<0.0001 for both doses of SEK versus PBO). At week 24, the ACR50 response rate was 30.7% (62/202) for the SEK 75 mg group and 34.7% (70/202) for the SEK 150 mg arm compared with 7.4% (15/202) for the PBO group.

Radiographic data at 24 weeks

Using the FAS cohort and linear extrapolation of missing data, the pooled dose SEK cohort was statistically better in preventing the progression of structural damage as observed by the mean change from baseline to week 24 in the total vdH-mTSS – refer to Table 10. The vdH-mTSS was significantly lower in the SEK pooled dose group (n=366; mean change of 0.08 from baseline score of 21.4) compared to the PBO arm (n=179; mean change of 0.57 from baseline score of 28.4). The treatment related comparison estimate is -0.50, which is statistically significant (p=0.0113). In addition, both doses of SEK were statistically superior to PBO for the mean change from baseline to week 24 in the vdH-mTSS using the FAS cohort – refer to Table 10. The total vdH-mTSS was significantly lower in the SEK 75 mg group (n=181; mean change of 0.02 from baseline score of 20.4) compared to PBO (n=179; mean change of 0.57 from baseline score of 28.4; treatment comparison estimate of -0.54; p=0.0132). The mean change from baseline in the total vdH-mTSS was also lower for the SEK 150 mg arm (n=185; mean change of 0.13 from baseline score of 22.3) versus PBO (treatment comparison estimate of -0.44; p=0.0212).

The difference between SEK and PBO therapy for structural progression was mainly explained by treatment related differences in the ES. At week 24, the mean change from baseline in the ES was low at 0.06 (baseline mean of 12.1) in the combined SEK group, whereas the ES worsened in the PBO arm by 0.35 (baseline mean of 16.3). The treatment related difference between the combined SEK and PBO groups for ES at 24 weeks was -0.31 (p=0.0152). At week 24, the mean change from baseline in the JSN score was near zero (i.e. indicating no significant progression of JSN) in the combined SEK group (mean change of 0.02 from baseline of 9.49) compared with 0.23 (baseline mean of 12.16) in the PBO arm. However, there was no statistically significant difference between the pooled SEK and PBO groups for JSN at 24 weeks (p=0.0594; mean treatment related estimate of -0.019).

Sensitivity analyses of the mean change from baseline to week 24 in total vdH-mTSS confirmed the integrity of the primary analysis. When 3 outlier results were removed (2 subjects in the PBO group and 1 in the SEK 75 mg arm), the mean change from baseline to week 24 was 0.38 (versus 0.57 in the primary analysis) for the PBO group and -0.06 (versus 0.02 previously in the primary analysis) for the SEK 75 mg arm. This did not alter the statistically significant result in favour of pooled SEK therapy versus PBO for the mean change from baseline to week 24 in the total vdH-mTSS. Another sensitivity analysis using the cohort of patients who were X-ray completers (i.e. had evaluable X-rays at baseline, and weeks 16-24 and 52) showed a similar result in favour of SEK therapy.

Radiographic results for the mean change from baseline in the total vdH-mTSS and JSN score were similar in each treatment group (both doses of SEK and PBO) irrespective of whether or

not subjects were anti-TNF experienced or naïve. However, the mean changes from baseline to week 24 in the ES were numerically lower (meaning less progression) for anti-TNF naive subjects in all 3 treatment groups. The treatment related difference with SEK versus PBO was statistically significant for the patients in the SEK 150 mg group (mean treatment related change from baseline to week 24 in ES was 0.28 for anti-TNF experienced subjects versus 0.48 for the anti-TNF naïve patients). Although SEK treated patients taking concomitant MTX had numerically lower total vdH-mTSS and ES in general, the treatment related difference between SEK and PBO for matched subjects was not statistically significant.

Dactylitis and enthesitis

At week 24, the SEK pooled dose cohort was superior to PBO for the incidence of dactylitis and enthesitis in the subset of patients who had these disease manifestations at baseline ($p<0.0001$ for SEK versus PBO for both soft tissue disease manifestations). At week 24, the incidence of dactylitis in the pooled SEK treatment group was 47.6% (99/208) compared with 84.5% (98/116) in the PBO arm. At week 24, the incidence of enthesitis in the pooled SEK treatment group was 52.5% (134/255) compared with 87.2% (102/117) in the PBO arm.

Clinical efficacy outcomes at week 52

The key exploratory efficacy endpoints of clinical relevance assessed at 52 weeks of treatment follow-up were the rates of ACR response (20, 50 and 70) and MCR. By week 52, the MCR rate using Fisher's exact test with NRI of the FAS cohort was 7.4% (15/202) for the SEK 75 mg group, 14.9% (30/202) for the SEK 150 mg arm and 2.5% (5/202) for the PBO group. The OR of achieving MCR at week 52 was statistically greater in the SEK 75 mg group versus PBO (OR=0.32 [95% CI 0.088, 0.941]; p=0.0365) as well as in the SEK 150 mg arm versus PBO (OR=0.15 [95% CI 0.043, 0.392]; p<0.0001).

The data from the FAS cohort up to week 52 (using NRI) showed that both doses of SEK maintained the rate of ACR20 response: 56.9% (115/202) for SEK 75 mg therapy and 59.9% (121/202) for SEK 150 mg injections. In the PBO group, where all patients were switched to SEK by week 24, the overall rate of ACR 50 response increased from 17.3% (35/202) at week 24 to 45.0% (91/202) at week 52.

Both doses of SEK demonstrated maintenance or improved rates of ACR50 response at week 52 in the FAS cohort using observed data. At week 52, the ACR50 response rate was 38.4% (66/172) for patients who continuously received SEK 75 mg injections and 50.0% (87/174) for the group who received SEK 150 mg from randomisation. In the PBO group, where all patients were switched to SEK by week 24, the overall rate of ACR 50 response increased from 7.4% (15/202) at week 24 to 44.4% (72/162) at week 52.

Similarly, both doses of SEK demonstrated maintenance or improved rates of ACR70 response at week 52 in the FAS cohort using observed data. At week 52, the ACR70 response rate was 25.6% (44/172) for patients who continuously received SEK 75 mg injections and 28.2% (49/174) for the group who received SEK 150 mg from randomisation. For comparison, the week 24 rate of ACR70 response was 19.3% (36/187) for patients in the SEK 75 mg group and 20.7% (39/188) for the SEK 150 mg arm. In the PBO group, where all patients were switched to SEK by week 24, the overall rate of ACR 70 response increased from 6.3% (11/174) at week 24 to 27.1% (44/162) at week 52.

Radiographic data at week 52

Joint structural damage changes from baseline up to week 52 according to original SEK dose treatment or PBO switch status are summarised in Table 11. At 52 weeks, continued treatment with SEK (both doses) from randomisation resulted in some progression in structural damage between weeks 24 and 52, but the overall mean change from baseline was relatively small in magnitude suggesting that SEK resulted in less disease progression than expected. At 52 weeks using the FAS cohort and linear extrapolation of missing data, SEK 75 mg injections resulted in a

mean change from baseline in the total vdH-mTSS of 0.22 (baseline mean of 19.96) and SEK 150 mg therapy produced a mean change from baseline of 0.37 (baseline mean of 21.94) – refer to Table 12. For both SEK doses, the mean change in vdH-mTSS between weeks 24 and 52 was more in magnitude (mean change of 0.20-0.24) than that observed between weeks 0 and 24 (mean change of 0.02-0.13). The mean increase in vdH-mTSS was predominately explained by increases in ES between weeks 24 and 52. The 2 year radiographic data for the patients who received SEK from the outset in this trial will be important to assess for determining maintenance of minimising structural progression with continued SEK therapy. For PBO patients who switched to SEK (either dose) between weeks 16 and 24, there was a significant blunting of increases in the total vdH-mTSS score between weeks 24 to 52 as a result of commencing SEK. For the 93 patients who switched from PBO to SEK 75 mg injections, the mean change in vdH-mTSS score only increased from 0.55 at week 24 to 0.57 at 52 weeks (i.e. mean progression of 0.02 between weeks 24 to 52). For the 94 patients who switched from PBO to SEK 150 mg injections, the mean change in vdH-mTSS score only increased from 0.53 at week 24 to 0.65 at 52 weeks (i.e. mean progression of 0.12 between weeks 24 to 52).

Table 12: Summary of Joint Structural Damage Change from Baseline to Week 52 in Study F2306.

	Secukinumab 10 mg/kg - 75 mg (n =202)		Secukinumab 10 mg/kg - 150 mg (n =202)		Placebo – secukinumab 75 mg (n =93)		Placebo – secukinumab 150 mg (n =94)	
Analysis visit	Base Mean (SD)	Change Mean (SD)	Base Mean (SD)	Change Mean (SD)	Base Mean (SD)	Change Mean (SD)	Base Mean (SD)	Change Mean (SD)
X-ray: Total vdH-S score								
Baseline	19.96 (38.816)		21.94 (47.540)		30.07 (70.135)		25.46 (55.442)	
[1]Week 24	20.40 (39.367)	0.02 (1.596)	22.26 (47.999)	0.13 (1.176)	30.99 (71.954)	0.55 (3.104)	25.46 (55.442)	0.53 (1.563)
[1]Week 52	19.96 (38.816)	0.22 (2.162)	21.94 (47.540)	0.37 (2.334)	30.07 (70.135)	0.57 (2.647)	25.46 (55.442)	0.65 (1.783)
X-ray: Erosion score								
Baseline	11.52 (22.312)		12.26 (27.130)		17.41 (41.326)		14.27 (32.381)	
[1]Week 24	11.72 (22.635)	0.08 (0.925)	12.44 (27.393)	0.04 (0.599)	17.90 (42.430)	0.38 (2.087)	14.27 (32.381)	0.29 (1.029)
[1]Week 52	11.52 (22.312)	0.21 (1.415)	12.26 (27.130)	0.21 (1.298)	17.41 (41.326)	0.42 (1.961)	14.27 (32.381)	0.38 (1.124)
X-ray: Joint spacing narrowing score								
Baseline	8.89 (18.191)		9.68 (21.091)		12.66 (29.413)		11.19 (23.462)	
[1]Week 24	9.15 (18.432)	-0.06 (0.932)	9.82 (21.294)	0.10 (0.957)	13.09 (30.139)	0.17 (1.283)	11.19 (23.462)	0.24 (1.051)
[1]Week 52	8.89 (18.191)	0.01 (1.033)	9.68 (21.091)	0.16 (1.312)	12.66 (29.413)	0.15 (0.909)	11.19 (23.462)	0.28 (0.943)

[1] linear extrapolation
Base = Baseline, Post = Post-baseline, Change = Post – Base.
Baseline is defined as the last observation on the day of or before the first dose of study drug, or the first observation within 30 days post dosing when no observation available prior to dosing.
At each time point, only subjects with a value at both baseline and that time point are included.

The sponsor has provided a supporting analysis of the radiographic data at 52 weeks using the number of subjects for which no disease progression (defined as ≤0 change from baseline in the total vdH-mTSS) was recorded. At week 52 using logistic regression and linear extrapolation of the FAS, 75.5% (284/376) of subjects in the pooled SEK group showed no X-ray progression versus 62.5% (115/184) of patients in the PBO arm. The number of responders was statistically significant for the comparison between the SEK 75 mg (79.7%; 149/187) and PBO groups

(p=0.0004) but not for the comparison of the SEK 150 mg dose (71.4%; 135/189) versus PBO (p=0.0767).

Using logistic regression with linear extrapolation in the FAS, the same pattern of findings was observed for the percentage of subjects with no X-ray progression at 24 weeks. In the pooled SEK cohort, 79.5% (291/366) of subjects showed no X-ray progression versus 70.4% (126/179) of patients in the PBO arm (p=0.0178). The number of responders was statistically significant for the comparison between the SEK 75 mg (85.1%; 154/181) and PBO groups (p=0.0014) but not for the comparison of the SEK 150 mg dose (74.1%; 137/185) versus PBO (p=0.4937).

Similar findings were revealed when the sponsor did an analysis of the percentage of subjects with no disease progression using a higher cut-off threshold for the change from baseline in vdH-mTSS (≤0.5) in the cohort of X-ray completers between randomisation and week 24, and between weeks 24 and 52 – refer to Table 13. The percentage of subjects with ≤0.5 change from baseline in the vdH-mTSS was highest in the SEK 75 mg group between randomisation and week 24 (92.3%; 156/169). However, the higher dose of SEK (150 mg) did not achieve a statistically greater level of response compared with PBO between randomisation and week 24 (p=0.3763).

Table 13: Proportion of Subjects with ≤0.5 Change in vdH-mTSS from Randomisation to Week 24 and Between Weeks 24 and 52 in Study F2306 (X-ray Completer Dataset).

	Randomization – Week 24	Week 24 – Week 52	
Treatment Group	**n/M (%)**	**n/M (%)**	**p-value**
AIN457 10 mg/kg - 75 mg (N = 202)	156/169 (92.3)	145/169 (85.8)	0.0278
AIN457 10 mg/kg - 150 mg (N = 202)	144/175 (82.3)	150/175 (85.7)	0.3763
Placebo (N = 202)	115/152 (75.7)	132/152 (86.8)	0.0131

X-ray completers are those subjects that had X-ray measures at baseline, Week 16/24, and Week 52.
No disease progression from randomization is defined as a change in van der Heijde total modified Sharp score at Week 24 (with linear extrapolation) relative to baseline <= 0.5
No disease progression from Week 24 to Week 52 is defined as a change in van der Heijde total modified Sharp score from Week 24 (with linear extrapolation) to Week 52 (evaluable) <= 0.5 P-values are from McNemar's test.

The change from baseline to week 52 in radiographic endpoints was also analysed according to prior anti-TNF status (naïve versus experienced) and concomitant MTX use (yes/no). Joint structural damage change from baseline to week 52 was not affected by prior anti-TNF status. However, patients treated with SEK 150 mg injections receiving concomitant MTX had numerically lower (meaning less progression) total vdH-mTSS and ES, and the treatment related difference between SEK 150 mg therapy and PBO for matched subjects was statistically significant for the total vdH-mTSS.

Study F2312

Although Study F2312 achieved its pre-specified primary efficacy outcome, the statistical testing hierarchical sequence was terminated at the first secondary efficacy endpoint analysis (SEK 75 mg versus PBO for rate of PASI75 response at week 24) – refer to Table 14. Based on adjusted p-values, Study F2312 demonstrated that SEK 300 mg therapy was superior to PBO at week 24 for all secondary efficacy endpoints. For SEK 150 mg injections compared to PBO, all secondary efficacy outcomes were met with the exception of the mean change from baseline in the HAQ-DI score and the rate of ACR50 response at 24 weeks. The treatment effect of SEK 150 mg injections versus PBO for the rate of ACR50 response was identical to that observed in the SEK 300 mg cohort, but it was not tested because the ACR50 response rate was placed after HAQ-DI in the statistical testing hierarchy and the mean change from baseline in HAQ-DI did not achieve statistical significance for the SEK 150 mg dose versus PBO. None of the secondary efficacy endpoints were achieved for the comparison between SEK 75 mg therapy and PBO injections. In addition, the pooled SEK cohort versus PBO was not tested for enthesitis and dactylitis as the testing sequence required all previous efficacy endpoints to be significant in order to proceed with testing. However, the sponsor has provided nominal p-values for the SEK

150 mg and 300 mg doses versus PBO that suggest treatment related benefit in managing enthesitis and dactylitis with the 2 higher doses of SEK.

Table 14: Results for Primary and Secondary Efficacy Endpoints based on Hierarchical Testing Sequence in Study F2312.

			p-value		
Hypothesis	Endpoint	Comparison	unadjusted	adjusted	Statistically significant?
H1	ACR20 at Week 24	AIN457 75mg vs Placebo	0.0200	0.0399	Yes
H2	ACR20 at Week 24	AIN457 150mg vs Placebo	<0.0001	<0.0001	Yes
H3	ACR20 at Week 24	AIN457 300mg vs Placebo	<0.0001	<0.0001	Yes
H4	PASI75 at Week 24	AIN457 75mg vs Placebo	0.1650	0.1650	No
H5	PASI75 at Week 24	AIN457 150mg vs Placebo	0.0006	0.0017	Yes
H6	PASI75 at Week 24	AIN457 300mg vs Placebo	<0.0001	<0.0001	Yes
H7	PASI90 at Week 24	AIN457 75mg vs Placebo	0.6421	0.6421	No
H8	PASI90 at Week 24	AIN457 150mg vs Placebo	0.0029	0.0057	Yes
H9	PASI90 at Week 24	AIN457 300mg vs Placebo	0.0002	0.0005	Yes
H10	DAS28CRP at Week 24	AIN457 75mg vs Placebo	0.3763	0.6421	No
H11	DAS28CRP at Week 24	AIN457 150mg vs Placebo	0.0008	0.0057	Yes
H12	DAS28CRP at Week 24	AIN457 300mg vs Placebo	0.0004	0.0013	Yes
H13	SF36-PCS at Week 24	AIN457 75mg vs Placebo	0.0482	0.6421	No
H14	SF36-PCS at Week 24	AIN457 150mg vs Placebo	0.0003	0.0057	Yes
H15	SF36-PCS at Week 24	AIN457 300mg vs Placebo	<0.0001	0.0013	Yes
H16	HAQ-DI at Week 24	AIN457 75mg vs Placebo	0.9195	0.9195	No
H17	HAQ-DI at Week 24	AIN457 150mg vs Placebo	0.0278	0.0555	No
H18	HAQ-DI at Week 24	AIN457 300mg vs Placebo	0.0013	0.0040	Yes
H19	ACR50 at Week 24	AIN457 75mg vs Placebo	0.0245	0.9195	No
H20	ACR50 at Week 24	AIN457 150mg vs Placebo	<0.0001	0.0555	No
H21	ACR50 at Week 24	AIN457 300mg vs Placebo	<0.0001	0.0040	Yes
H22	Dactylitis at Week 24	AIN457 pooled vs Placebo	0.0114	0.9195	No
H23	Enthesitis at Week 24	AIN457 pooled vs Placebo	0.0060	0.9195	No

AIN457=SEK

Skin outcomes

The 2 higher doses of SEK were statistically superior to PBO for the rate of PASI75 and PASI90 response at week 24 in the FAS. At week 24, the PASI75 response rate was 48.3% (28/58) for the SEK 150 mg group and 63.4% (26/41) for the SEK 300 mg arm compared with 16.3% (7/43) for the PBO group (p=0.0006 for SEK 150 mg versus PBO and p<0.0001 for SEK 300 mg versus PBO). The PASI90 response rate at 24 weeks was 32.8% (19/58) for the SEK 150 mg group and 48.8% (20/41) for the SEK 300 mg arm compared with 9.3% (4/43) for the PBO group (p=0.0029 for SEK 150 mg versus PBO and p=0.0002 for SEK 300 mg versus PBO). For the SEK 75 mg dose group, there was a statistically higher rate of PASI75 response compared to PBO at week 16 (34.0% [17/50] for SEK 75 mg versus 7.0% [3/43] for PBO; p=0.0222) but the treatment response to SEK 75 mg injections declined thereafter to lose statistical significance by week 24 (28.0% [14/50] for SEK 75 mg versus 16.3% [7/43] for PBO; p=0.1650). The SEK 75 mg dose did not achieve statistical superiority versus PBO for the rate of PASI90 response at either week 16 or 24. At week 16, the PASI90 response rate was 20.0% (10/50) for the SEK 75 mg group compared to 7.0% (3/43) for the PBO arm (p=0.0601). At week 24, the PASI90 response rate was 12.0% (6/50) for the SEK 75 mg group compared to 9.3% (4/43) for the PBO arm (p=0.6421).

Disease activity

Using the FAS cohort, SEK 150 mg and 300 mg therapy were superior to PBO for the LS mean change from baseline to week 24 in the DAS28-CRP score (p<0.01 for both SEK treatment comparisons with PBO). At week 24, the LS mean change from baseline in the DAS28-CRP score was -1.58 (n=91; baseline mean score=4.90) for the SEK 150 mg group and -1.61 (n=93; baseline mean score=4.76) for the SEK 300 mg arm compared with -0.96 (n=32; baseline mean score=4.71) for the PBO group. Changes in the SEK 75 mg arm (-1.12 from a baseline score of

4.71; n=87) were similar to that observed in the PBO group and did not reach statistical significance (p=0.3763).

Quality of life

At 24 weeks, statistically greater improvements in the LS mean change from baseline in the SF36-PCS score were reported for all 3 doses of SEK with an apparent dose response relationship (4.38 for the 75 mg dose group [n=91], 6.39 for the 150 mg arm [n=96] and 7.25 for the 300 mg group [n=96] compared to PBO (1.95 [n=33]; p<0.05 for all doses of SEK versus PBO). However, I was unable to locate the mean baseline SF36-PCS scores in the submission to interpret the relative change in this variable from baseline.

Physical functioning

Improvements in physical function and disability as measured by the LS mean change from baseline to week 24 in HAQ-DI score were statistically better with SEK 150 mg and 300 mg dosing versus PBO. In the SEK 150 mg group the LS mean change was -0.48 (n=95; baseline mean score=1.22) and -0.56 for the SEK 300 mg arm (n=95; baseline mean score=1.28) compared to -0.31 for the PBO group (n=33; baseline mean score=1.17). The response seen in the SEK 75 mg dose cohort (-0.32 from a baseline mean of 1.16; n=89) was similar to that observed in the PBO group for this outcome (p=0.9195).

ACR50 response

All 3 doses of SEK were superior to PBO for the rate of ACR50 response at week 24 in the FAS using NRI. At week 24, the ACR50 response rate was 18.2% (18/99) for the SEK 75 mg group and 35.0% (35/100) in both the SEK 150 mg and 300 mg arms compared with 7.1% (7/98) for the PBO group. The unadjusted p-values were <0.0001 for the 2 higher doses of SEK versus PBO and 0.0245 for SEK 75 mg versus PBO.

Dactylitis and enthesitis

At week 24, the SEK pooled dose cohort was superior to PBO for the incidence of dactylitis and enthesitis in the subset of patients who had these disease manifestations at baseline (using unadjusted p-values). At week 24, the percentage of patients with unresolved dactylitis in the pooled SEK treatment group was 53.2% (59/111) compared with 85.2% (23/27) in the PBO arm. At week 24, the incidence of enthesitis in the pooled SEK treatment group was 59.6% (112/188) compared with 78.5% (51/65) in the PBO arm.

Efficacy outcomes at Week 52

In this submission, the sponsor has not reported any efficacy outcomes at week 52 in Study F2312 as an insufficient number of subjects have completed this assessment time point with efficacy data.

7.1.2. Other efficacy studies

7.1.2.1. Studies A2206 and A2206E1 (Phase 2 PsA Study and its extension phase)

Design, conduct and objectives

Study A2206

This was a Phase 2, proof-of-concept, randomised, double-blind, PBO-controlled trial in adult patients with active PsA. It was conducted at 11 investigator sites in 3 countries (5 centres in Germany, 4 sites in UK and 2 centres in the Netherlands) between March 2009 and December 2010. The primary objective of Study A2206 was to evaluate the efficacy of SEK after two IV doses of 10 mg/kg (given 3 weeks apart – baseline and week 3) compared to PBO based on the proportion of subjects achieving ACR20 response at 6 weeks. There was a screening period of up to 28 days followed by an active treatment period of 6 weeks and a post-treatment follow-up phase, which extended to week 24 in the core study period. Subject assessments were

scheduled to occur weekly for the first 4 weeks after baseline, then every 2 weeks until week 12 and then monthly thereafter up until week 24. The trial protocol was amended 6 times, 3 of which occurred prior to patient enrolment. The first 3 amendments contained clarifications about the timing of assessments; inclusion, exclusion and early termination criteria; and study drug handling. Amendments 4 and 5 contained information relating to an early interim data analysis at 6 weeks when approximately half of the total enrolled patients had completed 6 weeks of follow-up. The last amendment was never implemented but wished to recruit an additional 105 subjects for investigation of 3 additional IV SEK induction dose strategies (3 x 30 mg/kg, 6 x 10 mg/kg and 6 x 1.5 mg/kg).

Study A2206E1

Patients who completed the core study period of Study A2206 were eligible to enter an open-label, non-randomised trial (Study A2206E1) in which all subjects were administered IV SEK 3 mg/kg every 4 weeks up until week 24 (part 1) with a possible extension of an additional 6 months of therapy (part 2). Study A2206E1 was conducted between June 2010 and November 2012. The primary objective of Study A2206E1 was to assess the safety and tolerability of continued SEK therapy, however, some efficacy outcomes were also collected as an exploratory objective.

Inclusion and exclusion criteria

Study A2206

To be eligible for inclusion in Study A2206, patients had to be at least 18 years of age with a diagnosis of PsA according to the CASPAR criteria. All subjects were required to have each of the following criteria: involvement of at least 3 swollen and tender peripheral joints, PtGA of disease activity ≥40 mm (on 100 mm VAS), inflammatory joint pain ≥40 mm (on 100 mm VAS), disease inadequately controlled on at least 1 conventional DMARD taken for at least 3 months at the maximal tolerated dose and RF testing ≤100 IU with negative anti-CCP antibody testing by ELISA.

Concomitant treatment with either MTX (up to 25 mg/week) or sulfasalazine was allowed in Study A2206 if the dose of therapy had been stable for at least 4 weeks prior to randomisation. Patients taking DMARDs other than MTX or sulfasalazine were required to cease such therapy for at least 4 weeks prior to randomisation (or 8 weeks if taking leflunomide and it is not removed by cholestyramine washout). The concomitant use of oral CS was permitted for subjects taking stable doses (prednisone [or equivalent] <10 mg/day) for at least 2 weeks prior to randomisation. No CS injections (intra-articular or parenteral) were permitted within 4 weeks of randomisation. Low potency topical CS was allowed as background therapy for psoriasis affecting the face, scalp and genital area. Concomitant NSAID was also permitted, provided subjects were on a stable dose for at least 4 weeks prior to randomisation. Patients who had previously received anti-TNF therapy were allowed to be included as long as such therapy had been ceased 2-3 months prior to baseline.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A patient with a history of infection requiring treatment within 2 weeks of baseline, and a history of blood donation or loss within 8 weeks prior to screening was to be excluded. A history of malignancy (except for excised basal cell skin cancers or cervical carcinoma in situ successfully treated) was also an exclusion criterion. Patients with active or history of clinically significant cardiac abnormalities such as left bundle branch block on ECG, atrial fibrillation, left ventricular dysfunction, symptomatic coronary artery disease or hospitalised in the preceding 6 months because of cardiac disease were also to be excluded.

Subjects were screened for Hepatitis B and C, HIV as well as latent TB at baseline. Subjects with active TB were excluded, but those with latent TB could be included after treatment according to local country guidelines was initiated. All patients were required to have a chest X-ray within

12 weeks prior to screening. Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases >2 x ULN, total serum bilirubin >2 x ULN, total white blood cell count <4.5 x 10^9/L or >11 x 10^9/L and platelet count <100 x 10^9/L.

Study A2206E1

To be included into the open-label extension trial, subjects had to participate up to and complete the week 24 study visit assessments of the preceding study (A2206). If a patient had discontinued from Study A2206 after the week 16 visit because of unsatisfactory therapeutic effect, then they were eligible to enter into Study A2206E1 provided they did so within 3 weeks of withdrawal and meet the same criteria for defining active PsA at baseline in Study A2206. All patients were re-tested for Hepatitis B and C virus, as well as HIV infection before commencing in Study A2206E1.

Study treatment, randomisation and blinding

Study A2206

In this trial, patients were randomised centrally in a ratio of 2:1 to IV SEK 2 x 10 mg/kg (2 infusions, 3 weeks apart on study day 1 and 22) or matching PBO infusions. SEK was supplied in 50 mg lyophilised vials and reconstituted with 1.2 mL of sterile water. The SEK concentrate solution was diluted in 5% glucose bags for IV infusion through a 0.2 micron in-line filter. Patients were monitored for up to 4 hours after their first infusion of SEK. Study A2206 was a double-blind trial with patients and investigators blinded to treatment allocation.

Study A2206E1

No randomisation or blinding was undertaken in Study A2206E1. All enrolling subjects were administered IV SEK 3 mg/kg every 4 weeks for 6-12 months in this open-label extension trial. In this trial, SEK was supplied in 150 mg lyophilised vials and reconstituted/infused in a manner similar to Study A2206.

Efficacy criteria

Study A2206

The primary efficacy outcome of Study A2206 was the ACR20 response rate at week 6.

There were a number of secondary efficacy outcome endpoints in Study A2206, which included:

- ACR20 response rate at other time points up to week 24,
- ACR50, ACR70 and PsARC responder rates at each time point up until week 24,
- Change from baseline in DAS28 score, EULAR response rate and proportion of patients in clinical remission (defined as DAS28 score $\leq$2.8) at weeks 6 and 12,
- Median change from baseline in CRP readings at week 6, and
- Changes in MASES, LDI and PASI scores over time to week 24.

The Psoriatic Arthritic Response Criteria (PsARC) contains a variation of 4 of the measures of the ACR20 response (Swollen and Tender joint counts; as well as the Physician's and Patient's Global Assessment of Disease Activity) but does not include a measure of pain, function/disability, or an acute phase reactant (ESR or CRP). PsARC response is defined as no worsening ($\geq$20% difference) in any of the criteria listed above, and an improvement from baseline in at least 2 of the 4 criteria, one of which has to be either the tender or swollen joint count.

Study A2206E1

The exploratory efficacy outcomes reported in this open-label, extension trial included the rates of ACR20, 50 and 70 response over time, the mean change from baseline in DAS28 score and the rates of good EULAR response achieved up to week 52.

Statistical considerations and sample size

Study A2206

The primary efficacy analysis population in Study A2206 included all subjects who received at least 1 dose of study medication, had evaluable efficacy data and no significant protocol deviations that may have impacted upon their efficacy assessments. The primary efficacy outcome was a treatment comparison between SEK and PBO for rate of ACR20 response at 6 weeks using Fisher's exact test. A one-sided test was considered appropriate and significance was set at an alpha level of 10%. Similar analyses were performed on the same population for the rate of ACR50, ACR70 and PsARC response at various time points. Descriptive statistics were used to summarise other variables such as change from baseline in DAS28, MASES, LDI and PASI scores.

Study A2206 chose a randomisation ratio of 2:1 to allow maximal information to be collected on subjects exposed to SEK whilst maintaining an acceptable level of statistical power. With an estimated sample size of 26 patients receiving SEK and 13 subjects in the PBO arm, the study had 88% power to detect a statistically significant difference between the 2 treatment groups in the proportion of ACR20 responders, assuming a response rate of 60% in the SEK treatment group and 15% in the PBO arm. The total sample size of 39 was increased by 3 subjects (i.e. to 42 patients in total) to allow for the estimated number of patient discontinuations and/or incomplete data.

Study A2206E1

Descriptive statistics were used to summarise efficacy variables over time and no inferential analyses of this data was performed. There was no sample size calculation for Study A2206E1.

Patient disposition and protocol deviations

Study A2206

A total of 42 subjects (28 in the SEK and 14 in the PBO group) were enrolled and randomised in Study A2206. A higher percentage of subjects in the PBO group (28.6%; 4/14) compared to the SEK arm (10.7%; 3/28) discontinued before week 24. One patient in each treatment group withdrew consent before week 24, and all other patients (2 in the SEK group and 3 in the PBO arm) who prematurely discontinued did so because of unsatisfactory therapeutic effect.

In Study A2206, a total of 40 protocol deviations were recorded in 36 subjects. Moreover, 5 patients (4 in the SEK group and 1 in the PBO arm) were excluded from the primary efficacy analysis because of significant protocol deviations that may have impacted their results. Three patients (including 1 in the PBO group) were excluded from the primary efficacy analysis because of lower than allowed PsA disease activity at baseline, another subject in the SEK arm was excluded because they received prohibited treatment (intra-articular CS injection) before week 6, and 1 female patient in the SEK group was excluded from the efficacy analysis because of a serious adverse event (identified as having breast cancer in situ in the first 3 weeks of the trial and did not receive the second SEK infusion).

Study A2206E1

A total of 28 patients enrolled in this extension study (19 previously received SEK in Study A2206 and 9 were in the PBO arm) and all received at least 1 dose of IV SEK 3 mg/kg in Study A2206E1. Despite a total of 93 minor protocol deviations affecting 15 subjects in Study A2206E1, only 1 of the 28 enrolled patients was excluded from the efficacy analysis because of a significant protocol deviation (given systemic CS injections on study days 85 and 234).

Most subjects (78.6%; 22/28) completed the extension phase. A total of 6 patients prematurely discontinued due to the following reasons: 4 subjects withdrew consent (all previously treated with SEK in Study A2206), 1 patient discontinued due to lack of therapeutic benefit (previously

treated with SEK in Study A2206) and another subject developed a serious adverse event of myocardial infarction (previously received PBO in Study A2206).

Baseline data

Study A2206

The 2 treatment groups were comparable for demographic characteristics. The majority of subjects enrolled in this trial were Caucasian (93%; 39/42) with a mean age of 47 years (range: 21-61 years). More than half (64%; 27/42) of all patients were female with a mean BMI of 30.4 kg/m^2 (range: 20.4-59.5 kg/m^2).

In terms of PsA disease activity at baseline, the mean numbers of tender and swollen joints were similar for both treatment groups at 22.6-23.5 (maximum of 78) and 8.3-9.5 (maximum of 76), respectively. The mean baseline DAS28-CRP scores were identical in the PBO and SEK treatment groups at 4.8 and the mean baseline CRP readings were similar at 9.1-9.8 mg/L. The vast majority of subjects (92%; 34/37) had co-existent skin psoriasis with a very low mean baseline PASI score of 3.1 (median 2.0). The average duration of PsA was similar in both treatment groups at 5.4-6.3 years. Less than half of all subjects had dactylitis (38%; 14/37) and enthesitis (43%; 16/37) at baseline. The mean baseline LDI (2.2) and MASES scores (3.1) were low and similar between the 2 treatment groups.

Just less than half of all subjects (49%; 12 in the SEK arm and 6 in the PBO group) were taking MTX at baseline. Regarding prior conventional DMARD exposure, 49% (18/37) had a history of MTX use and 5% (2/37) had previously tried sulfasalazine. About one third of all subjects (35%; 10 in the SEK arm and 3 in the PBO group) had a history of prior exposure to anti-TNF therapy. A small but dissimilar proportion of subjects in each treatment group were using systemic CS at baseline (29% [7/24] in the SEK arm versus 15% [2/13] in the PBO group). Furthermore, concomitant NSAID use was common (75%; 18/24) in the SEK arm but infrequent in the PBO group (8%; 1/13).

Study A2206E1

The 28 enrolled patients in this extension trial had a mean age of 46.3 years and all but 1 subject was of Caucasian ethnicity. The majority of subjects were female (61%; 17/28) with a mean BMI of 31.5 kg/m^2 (range: 19-59 kg/m^2). The baseline PsA characteristics at the start of the extension trial period included a mean tender joint count of 19.2, mean swollen joint count of 6.9, mean DAS28 score of 4.23 and a mean baseline CRP value of 8.42 mg/L. Most patients (81%; 22/27) had co-existing skin psoriasis with a very low mean PASI score of 2.64 (median 1.20).

Efficacy results

Study A2206

The primary efficacy endpoint of Study A2206 was not achieved. At week 6, the rate of ACR20 response was 39% (9/23) in the SEK group compared to 23% (3/13) in the PBO arm (p=0.2731).

Similarly, at week 6, the rates of ACR50, ACR70 and PsARC response were not statistically different (all p-values ≥0.39) between the SEK and PBO groups (17% [4/23] versus 8% [1/13] for ACR50 response, 9% [2/23] versus 0 for ACR70 response and 43% [10/23] versus 38% [5/13] for PsARC response). However, the onset of action with SEK was rapid with ACR20, ACR50 and PsARC responses occurring as early as 2 weeks, with numerically higher rates of response with SEK versus PBO at almost all time points up until week 24 – refer to Table 15.

Table 15: Summary of ACR and PsARC Response Rates over Time in Study A2206.

Visit	Assessment	AIN457 2x10mg/kg (N=24*)	Placebo (N=13*)
DAY8	ACR20 responders n (%)	4/23 (17%)	1/13 (8%)
	ACR50 responders n (%)	0/23 (0%)	0/13 (0%)
	ACR70 responders n (%)	0/23 (0%)	0/13 (0%)
	PsARC responders n (%)	6/22 (27%)	3/13 (23%)
DAY15	ACR20 responders n (%)	6/24 (25%)	2/12 (17%)
	ACR50 responders n (%)	3/24 (13%)	0/13 (0%)
	ACR70 responders n (%)	0/24 (0%)	0/13 (0%)
	PsARC responders n (%)	8/24 (33%)	2/13 (15%)
WEEK6	ACR20 responders n (%)	9/23 (39%)	3/13 (23%)
	ACR50 responders n (%)	4/23 (17%)	1/13 (8%)
	ACR70 responders n (%)	2/23 (9%)	0/13 (0%)
	PsARC responders n (%)	10/23 (43%)	5/13 (38%)
WEEK8	ACR20 responders n (%)	10/24 (42%)	3/13 (23%)
	ACR50 responders n (%)	7/24 (29%)	1/13 (8%)
	ACR70 responders n (%)	4/24 (17%)	0/13 (0%)
	PsARC responders n (%)	12/23 (52%)	5/13 (38%)
WEEK12	ACR20 responders n (%)	9/23 (39%)	2/13 (15%)
	ACR50 responders n (%)	5/23 (22%)	1/13 (8%)
	ACR70 responders n (%)	2/23 (9%)	1/13 (8%)
	PsARC responders n (%)	11/21 (52%)	2/13 (15%)
WEEK16	ACR20 responders n (%)	9/22 (41%)	3/11 (27%)
	ACR50 responders n (%)	6/22 (27%)	2/11 (18%)
	ACR70 responders n (%)	4/22 (18%)	1/11 (9%)
	PsARC responders n (%)	12/22 (55%)	4/11 (36%)
WEEK24/EOS	ACR20 responders n (%)	10/23 (43%)	2/11 (18%)
	ACR50 responders n (%)	4/23 (17%)	1/11 (9%)
	ACR70 responders n (%)	3/23 (13%)	1/11 (9%)
	PsARC responders n (%)	11/22 (50%)	4/11 (36%)

* Total numbers of patients may differ across time points because intermittent missing data were not imputed and left missing in the derivation (see Section 9.7.4.3).

There were no statistically significant differences between the SEK and PBO arms for the mean change from baseline in DAS28 scores over time. Good EULAR responses at 6 weeks were observed in 21.7% (5/23) of patients treated with SEK versus 9.1% (1/11) of subjects in the PBO group, and at 12 weeks the rates of good EULAR response were 33.3% (7/21) in the SEK group compared with 18.2% (2/11) in the PBO arm. At 6 weeks, clinical remission was achieved in 21.7% (5/23) of patients treated with SEK versus 9.1% (1/11) of subjects in the PBO group, and at 12 weeks the rates of clinical remission were 23.8% (5/21) in the SEK group compared with 9.1% (1/11) in the PBO arm.

The median baseline CRP reading was 4.9 mg/L in the SEK treatment group and consistent with the biological activity of SEK this reduced slightly by 6 weeks to a median of 3.0 mg/L. There was no significant change from baseline to 6 weeks in the median CRP value for the PBO group. Although most patients in Study A2206 had concomitant plaque psoriasis at baseline, the baseline PASI scores were very low (in both treatment groups) to allow any meaningful interpretation of treatment related change. Likewise, the baseline LDI and MASES scores were too low to permit meaningful interpretation of potential treatment related differences.

The study report also contained a post-hoc analysis of ACR20 response at 6 weeks based on prior anti-TNF exposure. Among patients with prior anti-TNF exposure (n=13), only 1 of 10 patients treated with SEK and 1 of 3 subjects in the PBO arm achieved ACR20 response at 6 weeks, suggesting a PBO-like response with SEK treatment in subjects with a history of anti-TNF exposure. This is considerably different to the observed results in the anti-TNF naïve cohort (n=23), whereby the rate of ACR20 response was 62% (8/13) in the SEK treated patients and 20% (2/10) in the PBO arm.

Study A2206E1

At 24 weeks of therapy in the extension trial, the following rates of ACR response were observed: 48.1% (13/27) for ACR20, 37.0% (10/27) for ACR50 and 29.6% (8/27) for ACR70. Clinical responses were generally maintained over 52 weeks of continued SEK therapy with the following rates of ACR response being recorded: 55.6% (15/27) for ACR20, 37.0% (10/27) for ACR50 and 22.2% (6/27) for ACR70.

At 24 and 52 weeks of continued SEK therapy in Study A2206E1, the mean baseline DAS28 score was approximately 3.5, which is a slight reduction from the baseline value of 4.23 at the commencement of the extension trial. At 24 weeks, the rate of good EULAR response was 47.6% (10/21) and this was largely maintained until week 52 (40.0%; 8/20).

7.1.2.2. Skin psoriasis studies with psoriatic arthritis as co-morbidity

Concomitant PsA was recorded at screening in 422 (of 2401) patients with moderate to severe plaque psoriasis enrolled in the 4 PBO-controlled PSOR trials that have been previously evaluated. These studies include: A2302 (ERASURE), A2303 (FIXTURE), A2308 (FEATURE) and A2309 (JUNCTURE). Unfortunately, the latter 2 PSOR studies did not collect appropriate information for arthritis related efficacy endpoints, so were not presented in this submission. PsA was also reported as a co-morbidity in 198 (of 966) subjects with moderate to severe plaque PSOR recruited into Study A2304 (SCULPTURE). However, the sponsor also excluded data from this trial in the PsA efficacy presentation of this submission because the study was not PBO-controlled.

In Study A2302, patients aged ≥18 years of age were randomised 1:1:1 to either SC SEK 150 mg injections, SC SEK 300 mg therapy or matching PBO injections; and in Study A2303, subjects were randomised 1:1:1:1 to SC SEK 150 mg every 4 weeks, SC SEK 300 mg therapy, PBO injections or SC etanercept 50 mg. In both of these Phase 3 PSOR studies, the baseline demographic and disease characteristics in the PsA cohort were balanced across the treatment groups. In both trials, patients received study treatment at baseline and weeks 1, 2, and 3 (loading regimen) followed by an injection every 4 weeks starting at week 4 through to week 48. At week 12 in Study A2303, PBO-treated patients not achieving a PASI75 response were re-randomised 1:1 to either SC SEK 150 mg injections or SC SEK 300 mg therapy. Patients in the etanercept arm received 50 mg twice per week from baseline to week 12, and 50 mg once weekly thereafter up to week 51. Both of the Phase 3 PSOR studies, did not collected data to compute ACR scores, however, PASI responses and HAQ-DI scores were collected.

Efficacy responses at week 12 in the subpopulation of patients in Studies A2302 and A2303 with moderate to severe plaque PSOR and concomitant PsA were similar to those reported for the PsA population in Studies F2306 and F2312. The response rates for PASI75, PASI90 and HAQ-DI were consistently higher for SEK 150 mg and SEK 300 mg SC therapy compared to PBO for both studies – refer to Table 16. Furthermore, SEK 300 mg therapy showed numerically higher efficacy responses for all of these endpoints compared to SEK 150 mg injections (in both Study A2302 and A2303).

Table 16: Week 12 Efficacy Data for Patients with concomitant Psoriatic Arthritis and moderate to severe Skin Psoriasis in Studies A2302 and A2303.

	CAIN457A2302				CAIN457A2303			
	Response rate of PASI 75	Response rate of PASI 90	Mean change in HAQ-DI©	% of patients with change of ≥0.3 HAQ-DI© (MCID)	Response rate of PASI 75	Response rate of PASI 90	Mean change in HAQ-DI©	% of patients with change of ≥0.3 HAQ-DI© (MCID)
150 mg	70%	44%	-0.18	26.7%	59%	39%	-0.19	31.7%
300 mg	68%	53%	-0.35	47.1%	72%	44%	-0.41	45.5%
Placebo	4%	0%	-0.08	21.5%	2%	2%	0.02	12.8%
Etanercept*	-	-	-	-	39%	18%	-0.29	38.2%

* EU Sourced

In addition, patients with moderate to severe plaque PSOR and concomitant PsA who received either dose of SEK showed greater improvements in physical functioning, as measured by the mean change from baseline to week 12 in the HAQ-DI score compared to PBO treated subjects. For both Study A2302 and A2303, the mean change from baseline in the HAQ-DI score at baseline was comparable for each treatment group across the 2 trials. In Study A2302, the mean change in HAQ-DI score at week 12 was -0.18 for SEK 150 mg therapy and -0.35 for SEK 300 mg injections compared with -0.08 in the PBO arm. In Study A2303, the mean change from baseline to week 12 in the HAQ-DI score was -0.19 for SEK 150 mg injections and -0.41 for SEK 300 mg therapy versus -0.29 for etanercept 50 mg and 0.02 for the PBO group. In PsA patients, a reduction of ≥0.3 points in the HAQ-DI score from baseline is considered the MCID. In Study A2302, the proportion of patients achieving the MCID at week 12 was 26.7% in the SEK 150 mg group and 47.1% in the SEK 300 mg arm compared with 21.5 % in the PBO group. In Study A2303, the proportion of patients achieving the MCID threshold at week 12 was 31.7% in the SEK 150 mg group and 45.5% in the SEK 300 mg arm versus 38.2% in the etanercept treatment group and 12.8% in the PBO arm.

Overall, the results from Studies A2302 and A2303 demonstrate that in patients with moderate to severe PSOR and concomitant PsA, treatment with SEK 300 mg achieved numerically higher outcomes (skin and joint) than treatment with SEK 150 mg, etanercept or PBO injections. Improvements in the HAQ-DI scores with SEK therapy were observed as early as week 4 and were sustained through to week 52 for both doses of SEK (150 mg and 300 mg injections given SC every 4 weeks after loading).

7.1.3. Analyses performed across trials (pooled & meta analyses)

The sponsor has provided an integrated data analysis of the PsA studies consisting of tables and figures which pool the data for demography and other study population characteristics, exposure to study medication and efficacy endpoints. The principal aim of the pooled dataset was to examine for subgroup variables, such as subject age (<65 years versus ≥65 years), gender and ethnicity; baseline subject weight categories (<90 kg versus ≥90 kg) and disease activity (DAS28-CRP, HAQ-DI and hsCRP); geographic region; baseline BSA affected by PSOR (<3%, ≥3%, <10% and ≥10%); concomitant MTX or CS use and prior anti-TNF use (yes/no) plus reason for stopping anti-TNF (primary or secondary efficacy failure or tolerability issue) and number of prior anti-TNF drugs (1 versus ≥2).

The findings from the subgroup analyses were consistent with those reported for the individual Phase 3 trial datasets. In particular, the findings supported the SEK 150 mg SC regimen as the main posology (and the SEK 300 mg SC dose being appropriate in particular subgroups) as these regimens were the most efficacious when considering all aspects of the disease including the arthritic and skin measures of PsA as well as physical functioning.

The key evidence from the integrated efficacy data analyses included:

- PsA patients with moderate to severe PSOR (i.e. ≥10% BSA skin involvement at baseline) have an increased rate of PASI75 and PASI90 response at 24 weeks with the SEK 300 mg injections (65.4% and 50.0%, respectively; n=26) compared to those who received SEK 150 mg therapy (50.0% and 28.1%, respectively; n=32), albeit small patient numbers.
- A similar observation was apparent for subjects with between 3% and 10% BSA involvement with PSOR at baseline. The PASI75 and PASI90 response rates at week 24 were 60.0% and 46.7%, respectively, for SEK 300 mg injections (n=15 subjects) compared with 46.2% and 38.5%, respectively, for SEK 150 mg therapy (n=26 subjects).
- Anti-TNF-IR patients showed consistently greater benefit in multiple efficacy endpoints (ACR20, ACR50 and ACR70 response rates, HAQ-DI response, as well as the rate of PASI75 and PASI90 response) from a 300 mg dose of SEK compared to the 150 mg dose of SEK. The reason for anti-TNF failure and the number of prior anti-TNF drugs (1 or 2 drugs) did not appear to influence the response to SEK 300 mg.
- The beneficial effect of SEK on the joint (ACR20 response) and skin manifestations (PASI75 and PASI90 responses) were similar in subjects with or without the concurrent use of oral CS.
- The beneficial effect of SEK on skin and joint manifestations was similar in subjects with or without the concomitant use of MTX.
- Patients weighing ≥90 kg had a higher rate of ACR20 response at week 24 with SEK 300 mg therapy (60.0%; 18/30) compared to SEK 150 mg injections (38.5%; 20/52) but the rates of ACR50 and ACR70 response plus the mean change from baseline in the DAS28-CRP score seen in those weighing ≥90 kg were similar across the 2 doses of SEK. Responses to a variety of outcome measures achieved with SEK 150 mg in patients weighing <90 kg were similar to that recorded with SEK 300 mg injections. As such, the sponsor is not recommending a modification in SEK dose based on subject weight.

7.2. Evaluator's conclusions on clinical efficacy for Indication 1

In support of the extension of treatment indication for SEK to include PsA, this submission contains data from 2 pivotal Phase 3 studies (F2306 and F2312), which are highly similar in design; as well as 1 supportive Phase 2 trial (A2206) of 24 weeks duration, which enrolled a total of 42 patients (24 of whom received 2 x IV doses of SEK 10 mg/kg, given 3 week apart). The Phase 2 trial also had an open-label extension period (A2206E1) of up to 52 weeks duration, which enrolled a total of 28 patients. In Study A2206E1, all subjects received IV SEK 3 mg/kg every 4 weeks.

Both of the Phase 3 studies are ongoing with interim study reports up to 52 weeks of treatment follow-up being included in this submission. [4]A total of 1003 patients were recruited into the 2 Phase 3 studies, of which 703 subjects received any dose of SEK (75 mg, 150 mg or 300 mg injections) in the first 16 weeks (i.e. the true PBO-controlled period). In both Phase 3 studies, ~40% of PBO treated patients at week 16 did not meet the EE criteria and continued on PBO injections up to week 24. At weeks 16 or 24, all continuing PBO treated subjects (91.4%; 275/301) were switched to SEK (75 mg, 150 mg or 300 mg SC injections every 4 weeks in the maintenance treatment phase). In total, ~95% of subjects completed their week 24 assessment and ~85% of patients completed 52 weeks of treatment follow-up in the Phase 3 program.

Both of the Phase 3 studies were randomised, double-blinded, PBO-controlled in design and enrolled adult patients with a confirmed diagnosis of PsA for at least 6 months according to the

[4] For Study F2312, the Week 24 CSR was included in the submission.

CASPAR criteria. Subjects were required to have moderate-severe disease activity at baseline with at least 3 or more swollen and tender peripheral joints, despite at least 3 months of conventional treatment with NSAID and/or conventional DMARD (mainly, MTX) and/or anti-TNF therapy. All subjects were required to have either active PSOR lesions at baseline or a documented history of skin and/or nail involvement with PSOR. The Phase 3 studies were highly similar in design with the main difference being the use of an IV loading dose of SEK in Study F2306 versus a SC loading dose strategy in Study F2312. Both of the Phase 3 trials examined the effect of 2 doses of SEK (75 mg and 150 mg injections, given every 4 weeks by SC injection in the maintenance treatment phase) compared to PBO. Study F2312 also included a third dose of SEK for evaluation (300 mg injections; given at the same frequency as other SEK doses). The baseline demographic and disease related characteristics of patients in the Phase 3 trials are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. Just over half of all patients were female, predominately of Caucasian ethnicity (>85%), and within the expected age range of 25- 65 years (mean age of 49 years). Over one fifth of all recruited subjects were a current smoker and the mean BMI was ~30 kg/m^2. Current smoking status and obesity are factors associated with a diminished response to treatment in PsA. However, there are some caveats to the generalisability of the treatment population. For example, both studies excluded patients who were at a significant risk of infection or malignancy, or who had various abnormal laboratory results at baseline (e.g. abnormal haematology or liver function tests). At randomisation, patients were stratified on the basis of whether they were anti-TNF naïve or anti-TNF-IR. In total, 31.7% (318/1003) of all subjects recruited into the Phase 3 AS program had a history of anti-TNF exposure. Randomisation was not stratified by MTX use at baseline and half of all subjects (50.1%; 503/1003) in the Phase 3 PsA studies were taking MTX during the trials at a median weekly dose of 15 mg.

This submission is seeking an indication in active PsA and is generally consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EU guideline EMEA/CPMP/EWP/438/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis" (effective 5 February 2008). However, the Phase 3 trials did not evaluate anti-TNF drugs as the active comparator, which was an issue raised by the TGA in the pre-submission meeting. Nonetheless, none of the other biological drugs (including ustekinumab and 5 anti-TNF drugs) currently registered in Australia for PsA have conducted head-to-head studies with other biological therapies. Furthermore, both of the Phase 3 SEK trials did include patients who had previously been exposed to anti-TNF drugs and those who were anti-TNF naive. For both Phase 3 studies, the choice of efficacy endpoints and statistical analysis were appropriately performed; and strategies to maintain blinding and randomisation procedures were suitable.

The primary efficacy endpoint in both Phase 3 studies was the ACR20 response rate at week 24. The pre-specified secondary efficacy endpoints (all evaluated at week 24) included measures of skin response (PASI75 and PASI90 response) as well as the change from baseline in disease activity (DAS28-CRP score) and physical functioning (HAQ-DI score); and health related QOL, notably the LS mean change from baseline in the SF-36 PCS score. Study F2306 also included an analysis of sequential plain X-ray data of the peripheral joints taken up to 52 weeks. Both the Phase 3 studies also provided clinical efficacy data up to week 52 in support of the maintenance of treatment effect.

In Study F2306, where IV loading with SEK 10 mg/kg at baseline, week 2 and week 4 was given to both SEK treatment groups, the primary efficacy endpoint of a statistically superior ACR20 response at 24 weeks was reached with both doses of SEK. Overall, 50.5% (102/202) of patients treated with SC SEK 75 mg every 4 weeks in the maintenance phase and 50.0% (101/202) of subjects treated with SC SEK 150 mg injections achieved this outcome versus 17.3% (35/202) of patients in the PBO group. In addition, both doses of SEK examined in Study F2306 were superior to PBO for all of the pre-specified secondary efficacy measures such as the rates of

PASI75 and PASI90 response at 24 weeks, as well as the mean change from baseline in the DAS-28 CRP and HAQ-DI scores plus rate of ACR50 response and the mean change from baseline in the SF36-PCS score. Overall, the study confirmed that SEK is effective in treating the symptoms and signs of active PsA as well as improving physical functioning and health related QOL. There were no significant differences at 24 weeks between the 2 SEK dosing regimens in Study F2306, but this probably reflects the impact of the high dose IV loading regimen in the first 4 weeks of the trial with efficacy endpoint analysis being primarily conducted at week 24.

Similarly, in Study F2312 (i.e. where no IV loading dose regimen was included) all 3 evaluated doses of SEK were statistically superior to PBO at week 24 for the primary efficacy endpoint. The rate of ACR20 response at week 24 was 29.3% (29/99) in the SEK 75 mg group, 51.0% (51/100) in the SEK 150 mg arm and 54.0% (54/100) in the SEK 300 mg arm versus 15.3% (15/98) in the PBO group. However, the magnitude of the treatment effect with SEK versus PBO was similar with the 2 higher doses of SEK (150 mg and 300 mg given every 4 weeks by SC injection) but considerably lower (i.e. <15% difference in response rates) for SEK 75 mg injection therapy compared to PBO. In addition, the statistical hierarchical testing strategy that controls for multiplicity of testing was terminated at the first ranked secondary efficacy endpoint (PASI75 response rate at 24 weeks) because SEK 75 mg therapy was not statistically better than PBO. Based on adjusted p-values, Study F2312 demonstrated that SEK 300 mg therapy was superior to PBO at week 24 for all pre-specified secondary efficacy endpoints. For SEK 150 mg injections compared to PBO, all secondary efficacy outcomes were met with the exception of the mean change from baseline in the HAQ-DI score and the rate of ACR50 response at 24 weeks. However, the treatment effect of SEK 150 mg injections versus PBO for the rate of ACR50 response (35.0% versus 18.2%) was identical to that observed in the SEK 300 mg cohort (35.0%). Overall, SEK 150 mg therapy given by SC loading (as observed in Study F2312) had a similar magnitude of efficacy for the primary and secondary endpoints compared to the IV SEK loading regimens examined in Study F2306, indicating the optimal response to SEK is achieved with the proposed 150 mg SC dosing posology (every 4 weeks in the maintenance phase) and no additional benefit with SEK was observed with IV loading.

In the Phase 3 PsA program, the concurrent use of MTX did not appear to impact upon the ACR20 response rate at 24 weeks in subjects receiving SEK 150 mg and 300 mg injections. However, in Study F2312 (but not in Study F2306, where IV loading was given), the ACR20 response was numerically higher when SEK was combined with MTX in those who were given SEK 75 mg injections. This data supports the sponsor claim of using SEK with or without MTX. Furthermore, in the anti-TNF-IR subgroup of subjects in Study F2312, a statistically higher rate of ACR20 response was only demonstrated with SEK 300 mg therapy (45.5%; 15/33) compared to PBO (14.3% [5/35]; p=0.0077). Treatment with SEK 75 mg (14.7%; 5/34) or SEK 150 mg injections (29.7%; 11/37) was not statistically better than PBO in the anti-TNF-IR cohort (p=0.9639 and p=0.1216, respectively). In the anti-TNF naïve subset, the 24 week ACR20 responder rate was statistically better in all 3 SEK dose groups versus PBO (36.9% [24/65] for SEK 75 mg [p=0.0075], 63.5% [40/63] for SEK 150 mg [p<0.0001] and 58.2% [39/67] for SEK 300 mg [p<0.0001] versus 15.9% [10/63] in the PBO group. This data supports the sponsor request to register the SEK 300 mg dose of therapy for PsA patients who are anti-TNF-IR. Although not stratified for at randomisation, high subject weight at baseline ($\underline{\geq}$100 kg versus <100 kg) also appeared to be associated with lower ACR20 response rate and only the 300 mg dose of SEK was able to achieve a statistically higher response compared with PBO. The sponsor has not requested a dosing modification for patients weighing ≥100 kg in the proposed treatment indication wording.

Although the sponsor at present is not seeking a formal radiographic claim in the SEK indication wording for PsA, the key summary X-ray data from Study F2306 has been included in the proposed PI. Sequential X-rays taken at baseline, week 24 and week 52 of treatment follow-up show that SEK therapy (both the 75 mg and 150 mg dose regimens) is associated with a statistically lower increase (worsening) from baseline in the total vdH-mTSS compared with

PBO, which is mainly explained by treatment related differences in the progression of the ES. As such, there is preliminary data to indicate that SEK appears to slow the progression of radiographic damage in the peripheral joints of patients with active PsA at baseline.

The efficacy data available at 52 weeks in both Phase 3 studies indicated that the majority of responding patients appear to maintain their treatment related benefit with continued SEK up to 52 weeks of follow-up. In addition, for PBO patients who switched to SEK at week 16 or 24, the rate of ACR20 responses observed at 52 weeks (i.e. 24-32 weeks after switching to active treatment) were similar to those achieved in the originally treated SEK cohort.

Although the primary efficacy endpoint of the supporting Phase 2 Study A2206 was not met (i.e. treatment with 2 IV doses of SEK 10 mg/kg given 3 weeks apart was not statistically superior to PBO for the ACR20 response rate at week 6 (39% [9/23] for SEK versus 23% [2/13] for PBO), various secondary clinical efficacy outcomes such as the rate of ACR20, ACR50 and PsARC response at other time points up to week 24 were numerically higher with SEK versus PBO in this proof-of-concept trial. Like the Phase 3 studies, the extension phase of this trial (A2206E1) showed that clinical efficacy was maintained in the majority of subjects up to 52 weeks with continued SEK therapy.

Overall, the data in this submission supports the efficacy of SEK therapy in the treatment of adult patients with moderate-severely active PsA, with or without concurrent NSAID and/or MTX. SEK 150 mg by SC injection (given weekly for the first 4 weeks and then every 4 weeks thereafter) is the optimal dosing regimen for the majority of adult patients with PsA. The sponsor has requested a higher dose of SEK therapy (300 mg injections) in patients who are anti-TNF-IR, which is supported by the data observed in Study F2312. In the anti-TNF naïve group of patients, the magnitude of response with SEK is similar to that observed in the pivotal studies, which supported the registration of anti-TNF therapies in PsA.

7.3. Indication 2: ankylosing spondylitis

7.3.1. Pivotal efficacy studies

7.3.1.1. Studies F2305 (MEASURE-1) and F2310 (MEASURE-2)

Study design, objectives, locations and dates

There were 2 pivotal Phase 3 trials in support of the application for the treatment of AS with SEK. Both of the Phase 3 studies were of similar design - randomised, double-blind, parallel-group, PBO-controlled trials in adult patients with active AS. The main differences between the 2 pivotal Phase 3 studies was the use of an IV loading dose in Study F2305 versus a SC loading dose in Study F2310. Both of the Phase 3 trials examined the effect of 2 doses of SEK (75 mg and 150 mg injections) compared to PBO.

Because the Phase 3 studies are highly similar in design and conduct, they will be considered together in this report with their important differences highlighted and results presented independently. Both of the Phase 3 studies had a screening phase of up to 4-10 weeks to assess eligibility prior to randomisation. In this submission, the pivotal clinical efficacy data up to week 52 was included for both studies, but the trial schema was for a total treatment period of 2 years in Study F2305 and up to 5 years in Study F2310. In both trials, clinical efficacy and safety assessments were performed at baseline; weeks 1, 2 and 4; and every 4 weeks thereafter up until week 52. In Study F2305, there was an imaging sub-study that collected radiographic (MRI and plain X-ray data of the spine and sacroiliac joints, as well as bone mineral density data). The main purpose of the radiographic data was to evaluate the rate of MRI observed disease progression in a subset of patients at selected study centres. In this subset of patients, MRI was

performed at baseline, as well as weeks 16 and 52. This submission contained MRI data collected up to week 16 in 105 anti-TNF naïve subjects enrolled in Study F2305.[5]

In Study F2305 (MEASURE-1), eligible patients were to be equally randomised at baseline into 1 of 3 treatment groups. The first 2 groups were to receive IV SEK 10 mg/kg at baseline, week 2 and week 4. At week 8, one of the SEK treatment groups continued with a SC maintenance regimen of SEK 75 mg injected every 4 weeks and the other SEK treatment arm received a SC maintenance dose of 150 mg every 4 weeks. The PBO treatment group received IV PBO at baseline, week 2 and 4; followed by SC PBO injections every 4 weeks starting at week 8.

In Study F2310 (MEASURE-2), eligible patients were to be equally randomised at baseline into 1 of 3 treatment groups: SEK 75 mg, SEK 150 mg and PBO injections. All injections were given by SC administration at baseline; weeks 1, 2, 3 and 4; and then every 4 weeks thereafter.

The design of both Phase 3 studies allowed for EE in PBO treated patients demonstrating insufficient improvement. This is appropriate for ethical reasons. At week 16, all subjects were classified as either being responders or non-responders based on whether or not they had achieved the primary outcome endpoint of ASAS20 improvement. In both trials, subjects in the PBO group who met EE criteria (i.e. non-responders) were re-randomised 1:1 to receive blinded therapy with either SEK 75 mg injections every 4 weeks or 150 mg injections every 4 weeks (by SC administration) commencing at week 20. Subjects already receiving SEK who met the EE criteria at week 16 continued to receive their originally assigned therapy in a blinded fashion. At week 24, all remaining subjects in the PBO cohort were re-randomised 1:1 to receive either SEK 75 mg injections every 4 weeks or 150 mg injections every 4 weeks (by SC administration).[6]

The primary objective of the Phase 3 AS study program was to demonstrate that the efficacy of at least 1 dose of SEK was superior to PBO at 16 weeks in treating the symptoms and signs of active AS in adult patients. The secondary efficacy objectives of the study program included the assessment of the effects of SEK upon other clinical outcomes as well as health related QOL.

Study F2305 was conducted at 65 investigator sites in 14 countries in Europe (9 centres in Germany, 6 each in Italy and Russia, 5 in Bulgaria, 4 each in UK and Belgium, 3 each in France and Turkey, and 2 in the Netherlands), North America (9 centres in USA and 3 in Canada), South and Central America (5 centres in Peru and 4 in Mexico) and Taiwan (2 sites). The first patient was enrolled in Study F2305 in October 2011 and the last patient assessment for the interim report included in this submission occurred in December 2013. A total of 3 protocol amendments were implemented in this trial. The first amendment was instituted before the commencement of patient enrolment, and the other 2 amendments occurred after. The amendments contained clarifications about the inclusion criteria, guidance on how missing data would be handled in the data analysis and an additional description about the statistical analysis plan. None of the amendments had the potential to have significantly impacted on the integrity of the results.

Study F2310 was conducted in 54 investigator sites in 13 countries, mostly in Europe (including 7 centres in Russia and 2-5 sites in Austria, Czech Republic, Finland, Germany, Italy, Netherlands, Spain, Switzerland, and the UK). There were also 15 study centres in North America (11 in USA and 4 in Canada) and 2 centres in Singapore. The first patient was enrolled in Study F2310 in October 2012 and the last patient assessment for the interim report included in this submission occurred in August 2014. Only 1 protocol amendment was implemented and this occurred after enrolment into the trial was complete, but before database lock. The amendment expanded the statistical hierarchy of efficacy endpoint testing to match Study F2305 and provided additional detail about the statistical analysis plan. The amendment did not significantly impair the integrity of the results.

[5] There was also 52 week data included.
[6] In Study F2310, all placebo patients were re-randomised to SEK at Week 16.

Inclusion and exclusion criteria

To be eligible for inclusion in either Phase 3 study, patients had to be at least 18 years of age with a diagnosis of AS according to the 1984 modified New York criteria, which requires prior documented radiological evidence of AS on plain X-rays (bilateral grade ≥2 or unilateral grade ≥3 sacroiliitis) with at least 1 of 3 clinical criteria (inflammatory low back pain of ≥3 months, limitation of lumbar spine movement and limitation of chest wall expansion). Subjects were required to have active disease at baseline with the BASDAI score being ≥4 (0-10) and spinal pain ≥4 cm by visual analogue scale (VAS) on a 0 to 10 cm scale. No qualifying baseline CRP reading was specified in the protocol.

Enrolling subjects were to have active disease despite current NSAID at the highest recommended dose for at least 3 months, or <3 months if there was a history of withdrawal from NSAID because of intolerance, toxicity or contraindications. Patients were allowed to continue taking stable NSAID therapy (non-selective or COX-2 inhibitors) as part of their study treatment if they were on a stable dose of NSAID for at least 2 weeks prior to randomisation. Non-biological DMARD treatment for at least 3 months (and stable dose for at least 4 weeks) prior to baseline with either sulfasalazine ≤ 3g daily or MTX 7.5-25 mg weekly were permissible. All patients taking concurrent MTX during the trials were required to take folic acid supplementation. Patients taking DMARDs other than MTX or sulfasalazine were required to cease such therapy for at least 4 weeks prior to randomisation (or 8 weeks if taking leflunomide and it is not removed by cholestyramine washout). In both of the Phase 3 studies, the concomitant use of oral CS was permitted for subjects taking stable doses (prednisone [or equivalent] <10 mg/day) for at least 2 weeks prior to randomisation.

Study F2305 planned to enrol 30% of subjects with therapeutic failure to anti-TNF drugs (maximum of 3 agents) to ensure a representative AS population was examined. Anti-TNF-IR (inadequate responder) status was defined as patients having active disease despite treatment with TNF inhibitors for at least 3 months at a stable dose or for at least 1 dose in the situation of lack of tolerance. Study F2310 aimed to have 40% of randomised subjects as being anti-TNF-IR (maximum of 3 prior anti-TNF drugs).[7] Biological therapy, other than with anti-TNF drugs, was an exclusion criterion in both studies. Prior treatment with anti-TNF drugs was to have been ceased at least 8-10 weeks prior to randomisation, with the exception of etanercept whereby 4 weeks was deemed acceptable.

Other exclusion criteria were highly similar to that outlined in the Phase 3 PsA studies. Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A past history of substance abuse within the last 6 months, infection requiring treatment within 2 weeks, and a history of blood donation or loss within 8 weeks prior to screening were to be excluded. A history of malignancy (except for excised basal cell skin cancers or actinic keratosis, colonic polyps that have been removed, or cervical carcinoma in situ successfully treated by surgery) was also an exclusion criterion. An additional exclusion criteria from the AS studies compared to the PsA trials was active inflammatory diseases other than AS that might confound the evaluation of efficacy, including inflammatory bowel disease and uveitis. Total ankylosis of the spine was also an exclusion criterion.

Subjects were screened for Hepatitis B and C, HIV as well as latent Tuberculosis (TB) at baseline. The screening for latent TB involved either skin testing with PPD or QuantiFERON TB-Gold testing. Subjects with active TB were excluded, but those with latent TB could be included after treatment according to local country guidelines was initiated. All patients were required to have a chest X-ray within 12 weeks prior to screening. Plans for administration of live vaccines during the study period or 6 weeks prior to randomisation were an exclusion criterion.

[7] The study specified that no more than 40% could be TNF-IR.

Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases >2 x ULN, total serum bilirubin >27 μmol/L, serum creatinine >1.5 mg/dL, total white blood cell count <3.0 x 10^9/L, platelet count <100 x 10^9/L and haemoglobin <8.5 g/dL.

Study treatments

In both Phase 3 AS studies, subjects were randomised in a 1:1:1 ratio to receive SEK 75 mg, SEK 150 mg or PBO injections. In Study F2305, IV loading of SEK 10 mg/kg was administered to both SEK treatment arms at baseline, week 2 and week 4. Patients in the PBO group received matching IV infusions at the same time. Starting at week 8, 1 group of SEK treated subjects received 75 mg injections SC every 4 weeks and the other SEK treatment arm received 150 mg SC injections every 4 weeks. Patients in the PBO received SC PBO injections at weeks 8 and 12. If they were classified responders at week 16, then they continued with SC PBO injections at weeks 16 and 20. If PBO patients were classified as non-responders at week 16, then they were re-randomised 1:1 to receive SC SEK 75 mg every 4 weeks or SC SEK 150 mg every 4 weeks up to 2 years. In Study F2310, all patients received SC therapy from the beginning with injections (depending on their treatment assignment) to be given weekly from baseline to week 4, and then every 4 weeks thereafter up until 5 years. PBO treated subjects could be re-randomised 1:1 to SEK 75 mg or 150 mg SC injections at either week 16 or week 24 depending on their ASAS20 responder status at week 16.[8]

In Study F2310, study treatments (including PBO injections) could be self-administered by SC injection from baseline. Patients did not self-administer SC therapy in Study F2305.

Less than half of all subjects self-administered study treatment on at least 1 occasion in the first 16 weeks. A slightly higher proportion of subjects in the SEK 150 mg group self-administered therapy (45.8%; 33/72) compared to the other 2 treatment groups (38.4% [28/73] in the SEK 75 mg arm and 43.2% [32/74] in the PBO group). Overall, self-administration of study treatment in Study F2310 was relatively low at 27-31% of study visits up to week 16. During the entire treatment period of up to 52 weeks, the percentage of patients who self-administered SEK injections increased to 57.3% (121/211) but for less than half of all visits (39.0%).

Only 2 concurrent non-biological DMARD treatments were permissible during the Phase 3 AS studies: sulfasalazine ≤ 3g daily or MTX 7.5-25 mg weekly (with folic acid supplementation). The doses of all continued DMARD therapy had to be stable for at least 4 weeks prior to baseline. The use of DMARD combination therapy was forbidden. Patients were also able to continue with low dose CS (maximum oral dose of 10 mg/day of prednisone or equivalent) if they had been receiving a stable dose for at least 2 weeks prior to baseline. Similarly, NSAID (including COX-2 inhibitors) could be continued if these treatments were stable for at least 2 weeks prior to baseline. Simple analgesia with drugs like paracetamol were permitted (except nil for 24 hours before scheduled efficacy assessment), but high potency opioid analgesia (e.g. methadone or morphine) was not allowed. No change in concurrent NSAID, CS or DMARD dose was permitted in the first 16 weeks of the study, except for documented safety reasons. Intra-articular CS injections for active AS were permitted after the first 16 weeks of the trial.

Efficacy variables and outcomes

The main efficacy variables were:

- Assessment of Spondyloarthritis International Society (ASAS) response criteria, and some of its components (the BASFI [Bath Ankylosing Spondylitis Functional Index] and BASDAI measures).
- Health related QOL assessment, principally the mean change from baseline in SF36-PCS score and the Ankylosing Spondylitis Quality of Life (ASQoL) index.

[8] In Study F2310, all patients were re-randomised at Week 16.

The primary efficacy outcome in both Phase 3 AS studies was the rate of ASAS 20 response at 16 weeks. Each individual dose of SEK was compared to PBO to determine treatment related benefit.

The pre-specified secondary efficacy outcomes in the Phase 3 AS studies (listed below in their sequential testing order; all endpoints were evaluated at week 16) included:

- ASAS 40 response rate,
- Change from baseline in high sensitivity CRP (hsCRP) expressed as a ratio of the post-baseline result compared to the baseline value,
- ASAS 5/6 response rate,
- LS mean change from baseline in the total BASDAI score,
- LS mean change from baseline in the SF36-PCS score,
- LS mean change from baseline in the ASQoL, and
- Rate of ASAS partial remission.

The exploratory efficacy endpoints of clinical relevance assessed up to 52 weeks were the rates of ASAS20 and ASAS40 response, including the maintenance of response in those who continuously received either dose of SEK therapy from randomisation as well as the response achieved in PBO subjects who switched to active treatment with SEK. Additionally, all other secondary efficacy variables (listed above) were collected and analysed up to week 52.

In general, the key efficacy endpoints in both Phase 3 AS studies use validated metrics that have served as the basis of previously published studies, prior regulatory approvals, and are consistent with published guidelines. The endpoints studied were relevant to assess the proposed indication of reducing the signs and symptoms of active AS.

The ASAS response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with AS using 4 main domains and 2 additional assessment domains (CRP and spinal mobility represented by BASMI lateral flexion). A patient with an ASAS 20 response has demonstrated an improvement from baseline of 20%, no single domain worsening of ≥20% and absolute increase of at least 1 unit on the 0-10 NRS (Numerical Rating Scale) in at least 3 of the following 4 main domains: Patient's Global Assessment of disease activity (PtGA), spinal pain score (on 0-10 NRS), function (represented by BASFI), and inflammation (the mean of questions 5 and 6 of the BASDAI, concerning morning stiffness intensity and duration). The ASAS 40 response criteria include the same criteria as ASAS 20, but with the use of a higher percentage improvement (40% versus 20%), as well as an absolute improvement of at least 1 unit on the 0-10 NRS in at least 3 of the 4 domains, and no worsening at all in the remaining domains. An ASAS20 response is considered to be the minimal clinically meaningful response in AS, and an ASAS40 response is considered to be of significant clinical benefit. An ASAS 5/6 improvement is achieved when there is $\geq$20% improvement in at least 5 domains of the composite index. ASAS partial remission is defined as an absolute value not above 2 units (on the 10 point scale) in each of the 4 main domains.

The BASFI is a validated, disease-specific tool for assessing physical function. The index comprises 10 items (occurring in the past week), which are rated on a scale of 0-10. The BASFI is the mean of the 10 scores, with lower scores indicating better physical function. The first 8 questions relate to functional anatomical limitations due to active spinal disease (e.g. question 1 asks "can you put your socks or tights on without help?"), and the final 2 questions evaluate a patient's ability to cope with everyday life. The MCID is a 1-unit improvement from baseline on the NRS.

The BASDAI is a validated, self-reported instrument consisting of 6 questions (all rated on a 10-unit horizontal NRS) relating to fatigue, spinal and peripheral joint pain and swelling, enthesitis,

and morning stiffness (both severity and duration) over the last week. To give each symptom equal weighting, the mean of the 2 scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0-50 score is divided by 5 to give a final 0-10 BASDAI score. Scores of 4 or more (out of 10) indicate active AS. An MCID of 1 on the NRS is used.

The BASMI characterises the spinal mobility of patients with AS. It consists of 5 clinical measures reflecting axial movement: cervical rotation, tragus to wall distance, lumbar flexion (modified Schober test), intermalleolar distance and lateral lumbar flexion. The mean of the 5 scores provides the final BASMI score with a range of 0-10. In the SEK AS program, the linear version of the BASMI was utilised.

Health related QOL was principally assessed using 2 instruments: SF36-PCS score (version 2) which has already been described in this evaluation report; and the ASQoL, which is self-administered questionnaire containing 18 items, each with a dichotomous yes (given 1 point) or no (assigned zero value) response. The score has a range of 0-18 with a lower score indicating better QOL. The items assess mobility, energy levels, self-care and mood/emotion. The recall period for the questionnaire is "at the moment".

There were also a large number of other exploratory efficacy outcomes (17 in total), but the 2 endpoints included in the proposed PI are the proportion of subjects achieving a BASDAI 50 response and the percentage of patients reaching ASDAS-CRP major improvement (both measured at 16 weeks). A BASDAI 50 response is defined as at least a 50% improvement (i.e. decreased score) in the total BASDAI score compared to baseline. ASDAS-CRP major improvement is defined as when the ASDAS (Ankylosing Spondylitis Disease Activity Score) improves from baseline by at least 2 points when using CRP (preferred method) as the measure of serum inflammation as opposed to ESR. A change of ≥1.1 in the ASDAS is considered to reflect a clinically significant improvement. The ASDAS is a composite index which is a validated way to assess disease activity in AS. Using a complex mathematical calculation, it combines 5 disease activity variables into a single score (range of 0-10) with better validity, enhanced discriminative capacity and improved sensitivity to change as compared to using single item variables. The 5 variables are severity of back pain, duration of morning stiffness, PtGA, peripheral joint pain and swelling, and CRP.

MRI scans of the spine and sacroiliac (SI) joints were performed at baseline and 16 weeks (+/- 2 weeks) in a subset of patients enrolled in Study F2305. Some of this information has been included in the proposed PI. Two independent readers using a standardized approach performed the MRI scoring. Readers were blinded to the order of the scans and treatment allocation. The mean change from baseline was assessed for sacroiliac joints using the Berlin SI-joint oedema score and spinal inflammation was evaluated using the Berlin modification of the ASspiMRI-a score (Braun and Baraliakos, 2011). The spinal scoring method quantifies bone marrow oedema changes in 23 vertebral units of the spine from the C2 to S1 vertebral body. Each vertebral unit is scored from 0-3, and the total score ranges from 0-69. Both trials are also assessing the rates of radiographic progression by plain X-rays taken at baseline and 2 years according to the mSASSS (modified Stoke Ankylosing Spondylitis Spine Score). The results of the plain X-ray evaluation are not yet available.

Randomisation and blinding methods

In both Phase 3 studies, subject randomisation was centrally conducted using interactive response technology (phone or web) and stratified by prior anti-TNF exposure (yes/no). In both trials, patients were allocated to treatment in a 1:1:1 ratio (SEK 75 mg, SEK 150 mg or PBO injections). PBO subjects who were classified as non-responders at week 16 were re-randomised in a 1:1 ratio (stratified by prior TNF antagonist exposure) to either SEK 75 mg or SEK 150 mg therapy. Subjects originally randomised to PBO who completed to week 24 were

re-randomised at that time point in a 1:1 ratio to either SEK 75 mg or 150 mg injections, again stratified by prior anti-TNF use.[9]

In both Phase 3 studies, each subject received a randomisation number, which was linked to a specified unique medication sequence communicated to an unblinded site pharmacist, who prepared the study treatment. Patients, investigator staff (with the exception of the site pharmacist), persons performing the assessments and data analysts remained blinded to the identity of study treatment from the time of subject randomisation until database lock (i.e. when all enrolling patients had completed their week 52 assessments).

Presumably, there are differences in the viscosity of SEK and PBO SC injections, and the submission did not specifically outline what special precautions may have been undertaken to limit this potential source of bias. The sponsor should be asked to outline what specific procedures were used to ensure blinding of SC administered study treatment in both the pivotal Phase 3 AS trials.

Analysis populations

In both studies, the primary analysis of all efficacy variables was performed using the FAS, which consisted of all subjects randomised into a trial to which study treatment was assigned. For sensitivity analyses of the primary efficacy variable, the Per-Protocol Set (PPS) was additionally explored. The PPS consisted of patients in the FAS who had received exposure to study medication without any major protocol deviations (e.g. unstable concomitant therapy or not meeting selection criteria) that may have affected the validity of the efficacy variables.

Sample size

Study F2305

The sample size calculations for Study F2305 were based on the results of a Phase 3 study by Inman et al (2008), which evaluated the efficacy of golimumab in adult patients with active AS. The PBO treatment group had an ASAS 20 response rate of 20% after 14 weeks in the anti-TNF naïve population. The ASAS 20 response rate at 16 weeks with SEK in this trial was estimated to be 60% in the anti-TNF naïve population, but lower in the anti-TNF-IR group. Study F2305 planned to have 30% of all recruited patients to have a history of past TNF exposure. For the primary endpoint of ASAS 20 response at 16 weeks, 116 patients per treatment group would yield 90% power to detect a treatment related difference with SEK versus PBO in Study F2305 (using Fisher's exact test). A 5% 2-sided type I error rate was used to control for type I error. Because 2 doses of SEK were examined in Study F2305, the type I error was split to 2.5% 2-sided for each SEK dose comparison versus PBO.

With the institution of a protocol amendment, the statistical hierarchy (primary plus ranked secondary efficacy variables) was expanded to evaluate additional efficacy endpoints. No adjustment of the sample size calculation was made for the updated statistical hierarchy. Nonetheless, for each of the pre-specified secondary clinical efficacy variables the estimated statistical power was >90% to detect a treatment related difference with at least 1 dose of SEK.

Study F2310

Study F2310 used the same published data and assumptions as Study F2305 to estimate the required sample size. An overall 5% 2-sided type I error rate was used to control for type I error. However, because 2 doses of SEK were examined in Study F2310, the type I error was split to 2.5% 2-sided for each SEK dose comparison versus PBO. The trial planned to recruit up to 40% of patients as being anti-TNF-IR. Based on the weighted average of the ASAS 20 response rates, 74 patients per treatment group would yield 99% power to detect a treatment related difference between SEK and PBO in Study F2310 (using Fisher's exact test).

[9] In Study F2310, all placebo patients were re-randomised at Week 16.

The study protocol also calculated the statistical power for each of the secondary clinical efficacy variables. The ASAS 40 response rate and the mean changes from baseline in hsCRP and SF36-PCS scores were all estimated to have >90% statistical power. The treatment related difference in ASAS 5/6 response and ASQoL at 16 weeks had 79-80% power to detect a treatment related difference between SEK and PBO.

Statistical methods

In both Phase 3 AS studies, a sequentially rejective testing strategy was used to evaluate the study hypotheses for the primary and secondary efficacy variables to protect the family-wise type I error rate at 5%, adjusting for multiplicity across the 2 SEK doses and endpoints. The statistical hypothesis for the primary efficacy outcome (ASAS20 response rate at week 16) being tested was that there was no difference between any of the SEK treatment regimens versus PBO.

For the secondary efficacy endpoints, a pre-defined statistical testing hierarchy was outlined:

- SEK (any dose arm) was no different to PBO for the ASAS40 response rate at week 16,
- SEK (any dose arm) was no different to PBO for the change in hsCRP at week 16,
- SEK (any dose arm) was no different to PBO for the rate of ASAS 5/6 improvement at week 16,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in total BASDAI score at week 16,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in SF36-PCS score at week 16,
- SEK (any dose arm) was no different to PBO for the improvement (change) from baseline in ASQoL score at week 16, and
- SEK (any dose arm) was no different to PBO for the rate of ASAS partial remission at week 16.

The primary efficacy endpoint of ASAS20 response at week 16 was analysed using a logistic regression model fitted with treatment and prior anti-TNF use (yes/no) as factors. Odds Ratios (OR) were computed for comparisons between SEK regimens versus PBO utilising the logistic regression model. Patients who discontinued from the trial (for any reason) prior to week 52 were considered non-responders. Similarly, subjects who did not have sufficient available data to compute the ASAS response at baseline or any time thereafter were also classified as non-responders. Sensitivity analysis using the observed data was also performed to support the integrity of the primary analysis. Other binary variables such as the rate of ASAS40 and BASDAI response were managed in the same manner as the ASAS20 analysis.

Continuous endpoints such as the change from baseline in hsCRP, BASDAI, SF-36 and ASQoL scores were evaluated using a mixed-effect model repeated measures with treatment regimen, prior anti-TNF use and visit as factors. An unstructured covariance structure was assumed for this model.

Participant flow

Study F2305

In Study F2305, a total of 448 subjects were screened for inclusion, of which 371 were randomised and included in the FAS (124 in the SEK 75 mg group, 125 in the SEK 150 mg arm and 122 in the PBO treatment group).

The most frequent reasons for discontinuation prior to randomisation (n=77 subjects) were screen failure (13.6% in total; 61/448) followed by subjects or guardian withdrawal of consent (2.0% in total; 9/448). Screen failure was due to a combination of not meeting inclusion criteria (n=20; mainly due to ineligible prior treatment [n=10]) and those with 1 or more exclusion

criterion (n=38; mainly due to history of chronic or recurrent infection, including latent TB [n=23]).

A total of 95.2% (577/606) of subjects continued until the week 16 assessment visit at a similar frequency in each of the 3 treatment groups: 96.0% (194/202) in the SEK 75 mg group, 97.0% (196/202) in the SEK 150 mg arm and 92.6% (187/202) in the PBO group. Expectedly, the proportion of subjects who met the criteria for EE at week 16 was substantially higher in the PBO group (65.8%; 123/202 – 61 received to SEK 75 mg and 60 received to SEK 150 mg injections [note: 1 re-randomised patient in each SEK group did not actually receive any SEK) compared to the SEK treatment groups (23.7% [46/202] in the 75 mg group and 26.0% [51/202] in the 150 mg dose arm).

Overall, 86.0% (319/371) of subjects completed 52 weeks of treatment follow-up in Study F2305: 83.6% (102/122) in the PBO group, 89.5% (111/124) in the SEK 75 mg arm and 84.8% (106/125) in the SEK 150 mg group. For the 52 subjects who had discontinued by week 52, the most common reasons were adverse events (20 patients), lack of efficacy (13 patients) and withdrawal of consent (12 subjects). All 3 reasons for premature discontinuation occurred at a similar frequency in the PBO and SEK treatment groups but discontinuations due to lack of efficacy were lower in the SEK 75 mg group (1.6% [2/124] versus 4.1-4.8% in the other 2 groups).

Of the 122 patients initially randomised into the PBO group, 10 discontinued before week 16 (i.e. while receiving PBO injections). A total of 112 PBO treated subjects were re-randomised at either week 16 or 24, and 9 of the week 16 non-responders withdrew from the trial after receiving SEK. A total of 77 PBO patients met the non-responder criteria at week 16, 39 of whom were re-randomised to SEK 75 mg injections and 38 patients were re-randomised to SEK 150 mg injections. Of the 35 patients who continued on PBO until 24 weeks, 17 were re-randomised to SEK 75 mg injections and 18 were re-randomised to SEK 150 mg SC injections every 4 weeks. The rates and reasons for discontinuation in treatment switch patients were similar to that observed in the continuously treated SEK cohorts.

Study F2310

In Study F2310, a total of 253 subjects were screened for inclusion, of which 219 (86.6%) were randomised and included in the FAS (73 subjects in the SEK 75 mg group, 72 in the SEK 150 mg arm and 74 in the PBO group). The 2 most frequent reasons for discontinuation prior to randomisation (n=34 subjects) were screen failure (10.3% in total; 26/253) followed by subject or guardian withdrawal of consent (2.4% in total; 6/253). Screen failure was due to a combination of not meeting inclusion criteria (n=13; due to either not meeting diagnostic criteria for AS [n=6] or insufficient prior anti-TNF use [n=5]) and those with 1 or more exclusion criterion (n=15; most commonly due to history of chronic or recurrent infection, including latent TB [n=5]).

A total of 200 subjects (91.3% of 219) continued until the week 16 assessment visit at a similar frequency in each of the 3 treatment groups: 93.2% (68/73) in the SEK 75 mg group, 91.7% (66/72) in the SEK 150 mg arm and 89.2% (66/74) in the PBO group. Of the 74 patients initially randomised into the PBO group, 66 were re-randomised at same stage in the trial, 32 to SEK 75 mg injections and 34 to SEK 150 mg therapy.

Overall, 82.6% (181/219) of subjects completed 52 weeks of treatment follow-up in Study F2310: 81.1% (60/74) in the PBO group, 82.2% (60/73) in the SEK 75 mg arm and 84.7% (61/72) in the SEK 150 mg group. For the 38 subjects who had discontinued by week 52, the 2 most common reasons were adverse events (13 patients) and lack of efficacy (13 subjects). Both reasons for premature discontinuation occurred at a similar frequency across the 3 treatment groups.

Major protocol violations/deviations

Study F2305

No patient was excluded from the FAS because of a protocol deviation; however, a total of 56 subjects (15.1% of 371) had documented protocol deviations that led to exclusion from the week 16 PPS analysis. These occurred at a slightly higher incidence in the 2 SEK treatment groups (15.3% [19/124] in the SEK 75 mg group and 16.0% [20/125] in the SEK 150 mg arm) compared with 13.9% (17/122) in the PBO group. The 2 most common reasons for protocol deviations resulting in exclusion from the PPS were "key procedures not performed as per protocol" (9.7% [12/124] in the SEK 75 mg group, 7.2% [9/125] in the SEK 150 mg arm and 5.7% [7/122] in the PBO group) and selection criteria not met (7.3% [9/124] in the SEK 75 mg group, 9.6% [12/125] in the SEK 150 mg arm and 5.7% [7/122] in the PBO group). All of the patient's excluded because of "key procedures not performed as per protocol" were as a result of study treatment being administered to subjects by unblinded site personnel and most (24/28) of the exclusions due to the selection criteria not being met were related to an insufficiently raised BASDAI score of $\geq$4 at baseline.

Up to week 16, a total of 88 subjects (23.7% of 371) had documented protocol deviations. These occurred at a higher incidence in the SEK 75 mg treatment group (27.4%; 34/124) compared to the other 2 treatment groups (22.4% [28/125] in the SEK 150 mg arm and 21.3% [26/122] in the PBO group). In addition, to the already detailed reasons resulting in exclusion from the PPS cohort, "GCP related deviations" were experienced on 5.6% (7/124) of patients in the SEK 75 mg group, 2.4% (3/125) of subjects in the SEK 150 mg arm and 5.7% (7/122) of patients in the PBO group; and use of prohibited concomitant medication was recorded in 6 patients (2 in the SEK 75 mg group and 4 in the PBO arm).

At 52 weeks, 32.3% (40/124) of subjects in the SEK 75 mg group, 25.6% (32/125) of patients in the SEK 150 mg arm and 25.4% (31/122) of subjects in the PBO group had at least 1 protocol violation recorded. The most common types of protocol violations recorded during the entire treatment period (across all treatment groups) were similar to that observed at week 16.

Study F2310

No patient was excluded from the FAS because of protocol deviation; however, a total of 10 subjects (4.6% of 219) had documented protocol deviations that led to exclusion from the week 16 PPS analysis. Two subjects were excluded from the PPS in the SEK 75 mg group (2.7% of 73), 5 subjects in the SEK 150 mg arm were excluded (6.9% of 72) and 3 patients (4.1% of 74) were excluded in the PBO group. The 2 most common reasons for exclusion from the PPS were selection criteria not met (6 patients in total; 4 in the SEK 150 mg group and 1 subject each in the SEK 75 mg and PBO arms) and treatment deviation (affecting 1 patient in each SEK dose group and 2 subjects in the PBO arm).

Up to week 16, a total of 62 subjects (28.3% of 219) had documented protocol deviations. These occurred at a similar frequency in the 3 treatment groups: 28.8% (21/73) in the SEK 75 mg group, 26.4% (19/72) in the SEK 150 mg arm and 29.7% (22/74) in the PBO group. The most commonly recorded reasons for protocol deviations were treatment deviations (12 patients in each SEK group and 16 subjects in the PBO arm), selection criteria not met (10 patients in total) and use of prohibited concomitant medication (10 subjects in total).

At 52 weeks, 34.2% (25/73) of subjects in the SEK 75 mg group, 29.2% (21/72) of patients in the SEK 150 mg arm and 33.8% (25/74) of subjects in the PBO group had at least 1 protocol violation recorded. The most common types of protocol violations recorded during the entire treatment period (across all treatment groups) were similar to that observed at week 16.

Baseline data

Study F2305

There were no clinically significant differences between the 3 treatment groups at baseline with respect to demographic characteristics. Enrolled subjects had a median age of 41.8 years (range: 18-76 years) with 95.4% of all subjects (354/371) expectantly being <65 years. More than two thirds of all subjects (69.3%; 257/371) were male, and just over half (60.9%; 226/371) were of Caucasian ethnicity. The overall population had a mean BMI of 26.5 kg/m^2 (range: 14.7-46.1 kg/m^2). Almost one quarter of all recruited subjects (23.7%; 88/371) was current smokers.

The treatment groups were also reasonably well balanced with respect to baseline disease features. The mean (and median) time since diagnosis of AS was 7.94 (4.99) years in the SEK 75 mg group, 6.54 (4.09) years in the SEK 150 mg arm and somewhat longer in the PBO group at 8.34 (5.84) years. Regarding the clinical features of AS at baseline, all but 2 subjects (1 in each of the SEK treatment groups) recorded inflammatory back pain of $\geq$3 months duration, 89.2% (331/371) had limitation of lumbar movement, 68.7% (255/371) had evidence of limited chest expansion, 20.2% (75/371) had grade 3-4 unilateral sacroiliitis on plain X-ray and 89.8% (333/371) had bilateral grade 2-4 sacroiliitis on X-ray. HLA-B27 was positive in the majority of subjects (74.1%; 275/371).

In terms of disease activity at baseline, the mean baseline BASDAI, BASMI and BASFI scores were similar for the 3 treatment groups. The mean BASDAI score was 6.05 for the SEK 75 mg group, 6.35 for the SEK 150 mg arm and 6.51 for the PBO group. The mean BASFI score was 5.39 for the SEK 75 mg group, 5.64 for the SEK 150 mg arm and 5.82 for the PBO group. The mean linear BASMI score was 4.21 for the SEK 75 mg group, 3.91 for the SEK 150 mg arm and 4.07 for the PBO group. All of the above disease activity scores at baseline are consistent with moderate-severe AS activity. At baseline, the mean hsCRP level was similar in each of the 3 treatment groups at 16.91-17.63 mg/L.

In total, 27.0% (100/371) of subjects had received previous treatment with anti-TNF drugs, and history of this prior medication use was near identical in the 3 treatment groups. All but 4 of the subjects (3 in the SEK 150 mg group and 1 in the SEK 75 mg arm) with a history of anti-TNF exposure had only received 1 agent (mostly, adalimumab – 12.4% of subjects in total). In the anti-TNF experienced subjects, just over half reported a primary lack of efficacy and just over one quarter recorded a secondary lack of efficacy as their main reason for discontinuation. Almost two thirds of all subjects had a history of prior DMARD use with either MTX or sulfasalazine. However, the majority of subjects in each of the 3 treatment groups (85.2%; 316/371) were not taking MTX at randomisation. In those taking MTX (14.8%; 55/371), the mean weekly dose was 13.5 mg (median 12.5 mg). At randomisation, one third of all subjects (33.4%; 124/371) were taking sulfasalazine, which was equally observed across the 3 treatment groups. The majority (~95%) of subjects reported past NSAID use and 38.3% (142/371) had reported prior non-response to NSAID therapy. During Study F2305, concomitant NSAID use was recorded in just over half of all patients in the trial, mainly with etoricoxib (15.1%), diclofenac (12.4%), celecoxib (11.5%) and meloxicam (10.5%). Overall, use of concurrent CS was recorded in 13.5% (50/371) of patients, at a similar frequency in all 3 treatment groups. The mean (and median) daily dose of CS at baseline was 7.24 (5.5) mg.

Collectively, 24.3% (90/371) had a past history of significant eye disorders, mainly uveitis; and approximately one third of all subjects (32.1%; 119/371) reported gastrointestinal complaints at baseline, mainly gastritis, reflux disease or peptic ulcer disease. One fifth of all recruited subjects had a current or past history of hypertension and 7.1% (26/371) had recorded dyslipidaemia at baseline.

Study F2310

Across the 3 treatment groups in Study F2310, there were no clinically significant differences in baseline demographic characteristics. Enrolled subjects had a mean age of 43.3 years (median

44 years; range: 19-77 years) with 96.8% of subjects (212/219) being <65 years of age. More than two thirds of all subjects (69.9%; 153/219) were male, and the majority (95.4%; 209/219) were of Caucasian ethnicity. The overall population had a mean BMI of 27.5 kg/m^2 (range: 17.2-54.8 kg/m^2). Almost one third of all recruited subjects (32.9%; 72/219) were current smokers.

The treatment groups were also reasonably well balanced with respect to baseline disease features. The mean (and median) time since diagnosis of AS was 5.27 (2.75) years in the SEK 75 mg group, 6.98 (3.78) years in the SEK 150 mg arm and 6.37 (2.78) years in the PBO group. Regarding the clinical features of AS at baseline, all but 3 subjects (1 in the SEK 75 mg and 2 in the PBO group) recorded inflammatory back pain of $\geq$3 months duration, 88.6% (194/219) had limitation of lumbar movement, 65.3% (143/219) had evidence of limited chest expansion, 13.7% (30/219) had grade 3-4 unilateral sacroiliitis on plain X-ray and 92.2% (202/219) had bilateral grade 2-4 sacroiliitis on X-ray. HLA-B27 was positive in the majority of subjects (76.7%; 168/219).

In terms of disease activity at baseline, the mean baseline BASDAI, BASMI and BASFI scores were similar for the 3 treatment groups. The mean BASDAI score was 6.57 for the SEK 75 mg group, 6.59 for the SEK 150 mg arm and 6.78 for the PBO group. The mean BASFI score was 5.98 for the SEK 75 mg group, 6.22 for the SEK 150 mg arm and 6.10 for the PBO group. The mean linear BASMI score was 3.92 for the SEK 75 mg group, 3.61 for the SEK 150 mg arm and 3.91 for the PBO group. All of the above disease activity scores at baseline are consistent with moderate-severe AS activity. At baseline, the mean hsCRP level was higher in the SEK 150 mg treatment group at 25.8 mg/L compared to the 2 other treatment groups (15.33-15.71 mg/L).

In total, 38.48% (85/219) of subjects had received previous treatment with anti-TNF drugs, and history of this prior medication use was near identical in the 3 treatment groups. Only 1 subject in the SEK 150 mg group had received more than 1 prior anti-TNF drug. The most commonly received prior anti-TNF therapies were adalimumab (17.8% of subjects in total) followed by infliximab (9.6% of subjects in total) and etanercept (8.7% of subjects in total). Just over half of all subjects (52.5%) had a history of prior DMARD use, mainly with either MTX or sulfasalazine. However, the majority of subjects in each of the 3 treatment groups (88.1%; 193/219) were not taking MTX at randomisation. In those taking MTX (11.9%; 26/219), the mean weekly dose was 13.9 mg (median 15.0 mg). At randomisation, a minority of subjects (14.2%; 31/219) were taking sulfasalazine, which was equally observed across the 3 treatment groups. The majority (98.6%) of subjects reported past NSAID use. During Study F2310, concomitant NSAID use was recorded in just less than half of all patients in the trial, mainly with ibuprofen (15.6%), diclofenac (10.5%), naproxen (8.2%) and celecoxib (6.4%). Overall, use of concurrent CS was recorded in 8.2% (18/219) of patients, at a similar frequency in all 3 treatment groups. The mean (and median) daily dose of CS at baseline was 6.83 (5.0) mg.

Regarding significant co-morbidity, almost one third of all subjects (31.5%; 119/371) reported gastrointestinal complaints, mainly gastritis, reflux disease or peptic ulcer disease. One quarter of all recruited subjects had a current or past history of hypertension, 9.1% (20/219) had recorded dyslipidaemia at baseline and 3.7% (8/219) had uncomplicated diabetes.

Results for the primary efficacy outcome

Study F2305

Both doses of SEK were superior to PBO for the rate of ASAS20 response at 16 weeks: 59.7% (74/124) for SEK 75 mg therapy and 60.8% (76/125) for SEK 150 mg treatment versus 28.7% (35/122) for PBO ($p<0.0001$ for both comparisons of SEK versus PBO). Various sensitivity analyses of the primary efficacy endpoint, such as using multiple imputations to handle missing data and the per-protocol set, confirmed the robustness of the primary analysis.

Interactions between treatment and selected baseline demographic and disease characteristics were also explored. Of the baseline covariates tested, only subject weight showed a significant interaction with treatment upon ASAS20 response at 16 weeks ($p=0.0122$). Randomisation was

not stratified by subject weight. The difference in ASAS20 response rate in favour of SEK 75 mg versus PBO was consistent across the 3 defined subject weight categories (<70 kg, 70-90 kg and >90 kg). However, the comparative treatment related benefit of SEK 150 mg versus PBO decreased as subject weight increased – refer to Table 17.

Table 17: ASAS20 Response Rate at Week 16 in Study F2305 by Subject Weight at Baseline.

Treatment/Weight Group	< 70 kg	70 – 90 kg	> 90 kg
IV-75 mg	27/51 (53%)	30/47 (64%)	17/26 (65%)
IV-150 mg	40/52 (77%)	28/55 (51%)	8/18 (44%)
Placebo	7/40 (18%)	21/61 (34%)	7/21 (33%)

In addition, anti-TNF naïve subjects generally showed numerically higher rates of ASAS20 response at 16 weeks (60.0% [54/90] for SEK 75 mg, 66.3% [61/92] for SEK 150 mg and 32.6% [29/89] for PBO) compared with anti-TNF experienced subjects (58.8% [20/34] for SEK 75 mg, 45.5% [15/33] for SEK 150 mg and 18.2% [6/33] for PBO).

Study F2310

Treatment with SEK 150 mg SC every 4 weeks was statistically superior to PBO for the rate of ASAS20 response at 16 weeks: 61.1% (44/72) for SEK 150 mg therapy versus 28.4% (21/74) for PBO (p<0.0001; OR of 4.38 [95% CI 2.14, 8.96] for a treatment related difference between SEK 150 mg therapy versus PBO). However, therapy with SEK 75 mg SC every 4 weeks was numerically higher (41.1%; 30/73) than PBO, but this did not achieve statistical significance (p=0.0967). The OR for detecting a treatment related difference between SEK 75 mg and PBO was 1.82 (95% CI 0.90, 3.67). Supportive analyses of the primary efficacy endpoint using different methods of handling for missing data and the per-protocol set confirmed the beneficial effect of SEK 150 mg therapy versus PBO.

Interactions between treatment and selected baseline demographic (age, gender and weight) and disease characteristics (hsCRP level, HLA-B27 status, anti-TNF exposure, time since diagnosis of AS and MTX use at baseline) were also explored. None of the baseline covariates tested showed a significant interaction with treatment upon ASAS20 response at 16 weeks (p<0.10). The treatment related difference in ASAS20 response (~30% difference) in favour of SEK 150 mg versus PBO was consistent across the 3 subject weight categories (<70 kg, 70-90 kg and >90 kg) – refer to Table 18. However, the treatment related benefit of SEK 75 mg versus PBO was lost as subject weight reached >90 kg (versus ~20% treatment related for subjects weighing ≤ 90 kg).

Table 18: ASAS20 Response Rate at Week 16 in Study F2310 by Subject Weight at Baseline.

Treatment	< 70 kg	70 – 90 kg	> 90 kg
AIN457 75 mg	8/18 (44.4%)	18/36 (50.0%)	4/19 (21.1%)
AIN457 150 mg	11/17 (64.7%)	24/37 (64.9%)	9/18 (50.0%)
Placebo	4/16 (25.0%)	14/43 (32.6%)	3/15 (20.0%)

Similar to the findings observed in Study F2305, anti-TNF naïve subjects in Study F2310 generally showed numerically higher rates of ASAS20 response at 16 weeks (51.1% [23/45] for SEK 75 mg, 68.2% [30/44] for SEK 150 mg and 31.1% [14/45] for PBO) compared with anti-TNF experienced subjects (25.0% [7/28] for SEK 75 mg, 50.0% [14/28] for SEK 150 mg and 24.1% [7/29] for PBO).

Results for other efficacy outcomes

Study F2305

In addition to achieving the primary efficacy outcome, Study F2305 demonstrated that both doses of SEK (75 mg and 150 mg) were superior to PBO at week 16 for all secondary efficacy endpoints in the statistical testing hierarchy – refer to Table 19.

Table 19: Results for Secondary Efficacy Endpoints in Study F2305 as per Hierarchical Testing.

Variable	AIN457 10mg/kg - 75 mg N=124	AIN457 10mg/kg - 150 mg N=125	Placebo N=122
Primary endpoint: ASAS 20 response	59.7% (p<0.0001)	60.8% (p<0.0001)	28.7%
ASAS 40 response	33.1% (p=0.0003)	41.6% (p<0.0001)	13.1%
hsCRP (ratio: post-BSL/BSL)	0.45 (p<0.0001)	0.40 (p<0.0001)	0.97
ASAS 5/6 response	45.2% (p<0.0001)	48.8% (p<0.0001)	13.1%
BASDAI change from baseline	−2.34 (p<0.0001)	−2.32 (p<0.0001)	−0.59
SF-36 PCS change from baseline	5.64 (p<0.0001)	5.57 (p<0.0001)	0.96
ASQoL change from baseline	−3.61 (p<0.0001)	−3.58 (p<0.0001)	−1.04
ASAS partial remission	16.1% (p=0.0020)	15.2% (p=0.0033)	3.3%

BSL = baseline

ASAS response criteria

Both doses of SEK were superior to PBO for the rate of ASAS40 response at week 16 in the FAS (p<0.0001 for SEK 150 mg versus PBO and p=0.0003 for SEK 75 mg versus PBO). At week 16, the ASAS40 response rate was 33.1% (41/124) for the SEK 75 mg group and 41.6% (52/125) for the SEK 150 mg arm compared with 13.1% (16/122) for the PBO group.

Both doses of SEK achieved a significantly higher rate of ASAS 5/6 improvement at 16 weeks compared with PBO (p<0.0001 for both SEK dose comparisons versus PBO). At 16 weeks, the rate of ASAS 5/6 improvement was 45.2% (56/124) for the SEK 75 mg group and 48.8% (61/125) for the SEK 150 mg arm compared with 13.1% (16/122) for the PBO group.

The proportion of subjects achieving ASAS partial remission at week 16 was significantly higher in both SEK treatment groups (16.1% [20/124] for SEK 75 mg [p=0.0020] and 15.2% [19/125] for SEK 150 mg [p=0.0033]) compared to PBO (3.3%; 4/122).

Serum inflammation (hsCRP change from baseline)

The change from baseline in hsCRP was expressed as a ratio of the post-baseline result compared to the baseline value. With the ratio normalised to 1.0 at baseline, a ratio of <1 indicates lower post-baseline values, whereas a ratio >1 represents increased post-baseline values. Using the FAS cohort, both doses of SEK produced statistically lower hsCRP ratios at week 16 compared to PBO (p<0.0001 for both SEK treatment comparisons with PBO). At week 16, the hsCRP ratio was 0.45 (n=115; baseline mean hsCRP 17.63 mg/L) for the SEK 75 mg group and 0.40 (n=121; baseline mean hsCRP 17.04 mg/L) for the SEK 150 mg arm compared with 0.97 (n=107; baseline mean hsCRP 16.91 mg/L) for the PBO group.

Total BASDAI (disease activity index) change from baseline

Significantly greater improvements in disease activity as measured by the LS mean change from baseline to week 16 in the total BASDAI score was observed for both doses of SEK (p<0.0001 for both doses of SEK versus PBO). At week, the LS mean change from baseline in BASDAI score was

-2.34 for the SEK 75 mg group (n=116; baseline mean BASDAI score 6.05) and -2.32 for the SEK 150 mg arm (n=121; baseline mean BASDAI score 6.35) compared to -0.59 for the PBO group (n=108; baseline mean BASDAI score 6.51).

Quality of life

At 16 weeks, statistically greater improvements in the LS mean change from baseline in the SF36-PCS score were reported for both doses of SEK: 5.64 for the 75 mg dose group (n=118) with a baseline mean score of 37.6; 5.57 for the SEK 150 mg arm (n=122) with a baseline mean score of 36.8 compared to 0.96 for PBO (n=111) with a baseline mean score of 36.3 ($p<0.0001$ for both doses of SEK versus PBO).

Both doses of SEK showed statistically greater improvements in the ASQoL from baseline to week 16 ($p<0.0001$ for both doses of SEK versus PBO). At 16 weeks, the LS mean change from baseline in the ASQoL was -3.61 for the SEK 75 mg dose group (n=118; baseline mean score of 10.815), -3.58 for the SEK 150 mg arm (n=121; baseline mean score of 10.85) and -1.04 for PBO group (n=111; baseline mean score of 11.67).

Exploratory efficacy endpoints

The proportion of patients who achieved at least 50% improvement from baseline in the total

BASDAI score (i.e., BASDAI 50 response) was higher in both SEK dose groups compared with PBO at all time-points up to week 24. At Week 16, the rate of BASDAI 50 responders was 39.5% (49/124) for the SEK 75 mg group and 37.6% (47/125) for the SEK 150 mg arm compared with 8.2% (10/122) for the PBO group ($p<0.0001$ for both doses of SEK versus PBO).

The proportion of patients demonstrating a major improvement in ASDAS-CRP (i.e. an improvement from baseline of ≥2.0 units on a 10-point scale) was higher with each dose of SEK compared with PBO at all time-points up to week 16. At week 16, the proportion of patients with a major improvement in ASDAS-CRP was 25.8% (32/124) for the SEK 75 mg group and 31.2% (39/125) for the SEK 150 mg arm versus 1.6% (2/122) for the PBO group ($p<0.0001$ for both doses of SEK versus PBO).

Radiographic (MRI) data at 16 weeks

In a subset of 105 anti-TNF naïve patients (34 in the SEK 75 mg group, 38 patients in the SEK

150 mg arm and 33 in the PBO group) treated at selected sites, MRI of the spine and SI joints were performed at baseline and 16 weeks. The MRI analysis examined 3 variables: Berlin SI joint oedema score (for SI joints); and the ASspi-MRI-a score and Berlin spine score (for the spinal evaluation). A small number of TNF-IR patients (9 in the SEK 75 mg group, 2 in the SEK 150 mg arm and 2 in the PBO group) also underwent MRI assessments but these patients were not included in the analysis.

As summarised in Table 20, the change from baseline to week 16 in all 3 MRI variables was statistically greater for both doses of SEK compared with PBO ($p<0.05$ for treatment related comparisons of SEK with PBO), but the absolute change from baseline was numerically higher for SEK 75 mg therapy compared with SEK 150 mg, although it should be noted that SEK 150 mg group had significantly lower baseline spinal scores (for both the ASspi-MRI-a and Berlin spine score). The percentage change from baseline to week 16 was consistently greater with each dose of SEK compared to PBO for each of the 3 MRI variables. For the Berlin SI joint oedema score, a 63% decrease from baseline for the SEK 75 mg and 59% decrease for SEK 150 mg was observed compared with a 7% decrease for PBO. Regarding the total ASspi-MRI-a score, there was a 54% decrease from baseline in the SEK 75 mg arm and 42% decrease in the SEK 150 mg group compared with a 12% decrease from baseline in the PBO arm. The relative decrease over 16 weeks in the Berlin spine score was 50% in the SEK 75 mg group and 48% in the SEK 150 mg arm versus 12% in the PBO group.

Table 20: MRI Measurements at Baseline and Week 16 in the Subset of Anti-TNF naïve Subjects examined in the MRI Sub-study of F2305.

MRI variable	n	Baseline (mean ± SD)	Week 16 (mean ± SD)	Change from baseline (mean ± SD)	p-value for comparison vs. placebo
Berlin sacroiliac joint total edema score					
10 mg/kg – 75 mg (N=34)	30	1.67 ± 2.551	0.62 ± 0.971	−1.05 ± 2.090	0.0024
10 mg/kg – 150 mg (N=38)	32	2.22 ± 3.377	0.92 ± 1.783	−1.30 ± 2.170	0.0013
Placebo (N=33)	26	2.40 ± 3.240	2.23 ± 3.238	−0.17 ± 1.232	
Total ASspi-MRI-a score					
10 mg/kg – 75 mg (N=34)	30	6.37 ± 10.757	2.93 ± 6.403	−3.43 ± 6.315	0.0027
10 mg/kg – 150 mg (N=38)	32	2.70 ± 3.801	1.58 ± 3.869	−1.13 ± 1.675	0.0790
Placebo (N=33)	28	5.73 ± 9.748	5.07 ± 8.600	−0.66 ± 2.553	
Berlin spine score					
10 mg/kg – 75 mg (N=34)	30	5.02 ± 7.580	2.48 ± 5.410	−2.53 ± 4.096	0.0063
10 mg/kg – 150 mg (N=38)	32	2.23 ± 2.826	1.16 ± 2.474	−1.08 ± 1.403	0.0570
Placebo (N=33)	28	4.50 ± 7.617	3.95 ± 6.820	−0.55 ± 2.447	

Clinical efficacy outcomes at Week 52

The key exploratory efficacy endpoints of clinical relevance assessed up to 52 weeks were the rates of ASAS20 and ASAS40 response, but all other secondary efficacy variables including the rate of ASAS 5/6 improvement and partial remission; as well as the LS mean change from baseline in the total BASDAI score were analysed.

The rates of ASAS20 and ASAS40 response observed for both SEK dose groups at week 16 were sustained or improved upon through to week 52. In addition, ASAS20 and ASAS40 response rates were comparable between the 2 SEK dose groups at all analysis visits through to week 52. By week 52, the rate of ASAS20 response using Fisher's exact test with NRI of the FAS cohort was 62.1% (77/124) for the SEK 75 mg group and 63.2% (79/125) for the SEK 150 mg arm. In the PBO treated patients who switched to SEK 75 therapy the rate of ASAS20 response at 52 weeks was 62.5% (35/56) and in the patients who commenced SEK 150 mg it was 60.7% (34/56). At week 52, the ASAS40 response rate was 42.7% (53/124) for patients who continuously received SEK 75 mg injections and 51.2% (64/125) for the group who received SEK 150 mg from randomisation. In the PBO group, where all patients were switched to SEK by week 24, the overall rate of ASAS40 response increased from 14.3% (16/112) at week 16 to 43.8% (49/112) at week 52.

There were no treatment differences between the 2 SEK dose groups through to week 52 in any of the other secondary efficacy variables, including ASAS 5/6 improvement, ASAS partial remission, and changes from baseline in hsCRP, total BASDAI, SF-36 PCS and ASQoL scores. Comparable levels of response were sustained between weeks 24 to 52 in both SEK groups.

Study F2310

SEK 150 mg therapy was superior to PBO at week 16 for all primary and secondary efficacy endpoints tested in the hierarchical hypothesis testing strategy apart from the rate of ASAS partial remission – refer to Table 21. However, treatment with SEK 75 mg injections was not statistically superior to PBO for any of the ranked primary and secondary efficacy outcomes.

Table 21: Results for Secondary Efficacy Endpoints in Study F2310 as per Hierarchical Testing.

Variable	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Primary endpoint: ASAS 20	41.1% (p=0.0967)	61.1% (p=0.0001)*	28.4%
ASAS 40	26.0% (p=0.0967)	36.1% (p=0.0008)*	10.8%
hsCRP (ratio: post-BSL/BSL)	0.61 (p=0.0967)	0.55 (p=0.0008)*	1.13
ASAS 5/6	34.2% (p=0.0967)	43.1% (p=0.0008)*	8.1%
BASDAI change from baseline	−1.92 (p=0.0967)	−2.19 (p=0.0008)*	−0.85
SF-36 PCS change from baseline	4.77 (p=0.0967)	6.06 (p=0.0008)*	1.92
ASQoL change from baseline	−3.33 (p=0.0967)	−4.00 (p=0.001)*	−1.37
ASAS partial remission	15.1% (p=0.0967)	13.9% (p=0.0941)	4.1%

BSL = baseline
* statistically significant adjusted p-values

ASAS response criteria

Treatment with SEK 150 mg was superior to PBO for the rate of ASAS40 response at week 16 in the FAS (p=0.0008), but this was not statistically demonstrated for SEK 75 mg therapy (p=0.0967) despite the rate of response being numerically higher. At week 16, the ASAS40 response rate was 36.1% (26/72) for the SEK 150 mg group and 26.0% (19/73) for the SEK 75 mg arm compared with 10.8% (8/74) for the PBO group.

Similarly, SEK 150 mg therapy, but not SEK 75 mg injections, achieved a statistically higher rate of ASAS 5/6 improvement at 16 weeks compared with PBO (p=0.0008 for SEK 150 mg versus PBO and p=0.0967 for SEK 75 mg versus PBO). At 16 weeks, the rate of ASAS 5/6 improvement was 43.1% (31/72) for the SEK 150 mg group and 34.2% (25/73) for the SEK 75 mg arm compared with 8.1% (6/74) for the PBO group.

Neither dose of SEK was statistically superior to PBO (p>0.094 for both doses of SEK versus PBO), when adjusting for the multiplicity of testing, for the proportion of subjects achieving ASAS partial remission at week 16. At 16 weeks, the rate of ASAS partial remission was 13.9% (10/72) for the SEK 150 mg group and 15.1% (11/73) for the SEK 75 mg arm compared with 4.1% (3/74) for the PBO group.

Serum inflammation (hsCRP change from baseline)

The change from baseline in hsCRP was expressed as a ratio of the post-baseline result compared to the baseline value. With the ratio normalised to 1.0 at baseline, a ratio of <1 indicates lower post-baseline values, whereas a ratio >1 represents increased post-baseline values. Using the FAS cohort, only the higher dose of SEK produced statistically lower hsCRP ratios at week 16 compared to PBO (adjusted p=0.0008 for SEK 150 mg treatment compared with PBO and p=0.0967 for SEK 75 mg versus PBO). At week 16, the hsCRP ratio was 0.61 (n=69; baseline mean hsCRP 15.33 mg/L) for the SEK 75 mg group and 0.55 (n=68; baseline mean hsCRP 25.8 mg/L) for the SEK 150 mg arm compared with 1.13 (n=66; baseline mean hsCRP 15.71 mg/L) for the PBO group.

Total BASDAI (disease activity index) change from baseline

The improvement in the total BASDAI score (LS mean change) from baseline to week 16 was statistically greater for SEK 150 mg (adjusted p=0.0008) compared to PBO, but not for SEK 75 mg versus PBO (adjusted p=0.0967). At week, the LS mean change from baseline in BASDAI score was

-1.92 for the SEK 75 mg group (n=67; baseline mean BASDAI score 6.57) and -2.19 for the SEK 150 mg arm (n=67; baseline mean BASDAI score 6.59) compared to -0.85 for the PBO group (n=64; baseline mean BASDAI score 6.78).

Quality of life

At 16 weeks, statistically greater improvements in the LS mean change from baseline in the SF36-PCS score was reported for SEK 150 mg (LS mean change of 6.06 from a baseline mean score of 34.4; n=67) compared with PBO (LS mean change of 1.92 from a baseline mean score of 36.2; n=66; p=0.0008). However, SEK 75 mg therapy was not associated with a statistically significant improvement from baseline in the SF36-PCS score (LS mean change of 4.77 from a baseline mean score of 36.2; n=66; p=0.0967) compared to PBO.

Likewise, only the higher dose of SEK produced a statistically greater improvement in the ASQoL from baseline to week 16 (p=0.001) compared to PBO. At 16 weeks, the LS mean change from baseline in the ASQoL was -3.33 for the SEK 75 mg dose group (n=66; baseline mean score of 11.36), -4.00 for the SEK 150 mg arm (n=66; baseline mean score of 12.15) and -1.37 for PBO group (n=66; baseline mean score of 11.50).

Exploratory efficacy endpoints

The proportion of patients who achieved at least 50% improvement from baseline in the total

BASDAI score (i.e., BASDAI 50 response) was higher in both SEK dose groups compared with PBO at all time-points up to week 16. At Week 16, the rate of BASDAI 50 responders was 24.7% (18/73) for the SEK 75 mg group and 30.6% (22/72) for the SEK 150 mg arm compared with 10.8% (8/74) for the PBO group (unadjusted p=0.004 for SEK 150 mg versus PBO and unadjusted p=0.0359 for SEK 75 mg versus PBO).

The proportion of patients demonstrating a major improvement in ASDAS-CRP (i.e. an improvement from baseline of ≥2.0 units on a 10-point scale) was higher with each dose of SEK compared with PBO at all time-points up to week 16. At week 16, the proportion of patients with a major improvement in ASDAS-CRP was 15.1% (11/73) for the SEK 75 mg group and 25.0% (18/72) for the SEK 150 mg arm versus 4.1% (3/74) for the PBO group (unadjusted p=0.0006 for SEK 150 mg versus PBO and unadjusted p=0.0126 for SEK 75 mg versus PBO).

Clinical efficacy outcomes at week 52

The key exploratory efficacy endpoints of clinical relevance assessed up to 52 weeks were the rates of ASAS20 and ASAS40 response, but all other secondary efficacy variables including the rate of ASAS 5/6 improvement and partial remission; as well as the LS mean change from baseline in the total BASDAI score were analysed.

The high rates of ASAS20 and ASAS40 response observed for both SEK dose groups at the week 16 were sustained or improved upon through to week 52. Furthermore, ASAS20 and ASAS40 response rates were numerically higher by ~10% in the SEK 150 mg dose group compared to the SEK 75 mg arm at all analysis visits through to week 52. By week 52, the rate of ASAS20 response using Fisher's exact test with NRI of the FAS cohort was 63.9% (39/61) for the SEK 75 mg group and 73.8% (45/61) for the SEK 150 mg arm. In the PBO treated patients who switched to SEK 75 therapy the rate of ASAS20 response at 52 weeks was 59.3% (16/27) and in the patients who commenced SEK 150 mg it was 75.0% (24/32).

At week 52, the ASAS40 response rate was 34.2% (25/73) for patients who continuously received SEK 75 mg injections and 48.6% (35/72) for the group who received SEK 150 mg from randomisation. In the PBO group, where all patients were switched to SEK by week 24, the overall rate of ASAS40 response increased from 12.1% (8/66) at week 16 to 47.0% (31/66) at week 52.

Overall, the treatment effect observed in the SEK 150 mg dose group was consistently higher than that seen in the SEK 75 mg group through to week 52 in all of the other secondary efficacy

variables, including ASAS 5/6 improvement, ASAS partial remission, and changes from baseline in hsCRP, total BASDAI, SF-36 PCS and ASQoL scores. However, within each SEK dose group, comparable levels of response were sustained between weeks 16 and 52.

7.3.2. Other efficacy studies

7.3.2.1. Study A2209 and A2209E1 (Phase 2 AS Study and its extension phase)

Design, conduct and objectives

Study A2209

This was a 2-part, proof-of-concept, randomised, double-blind, PBO-controlled trial in adult patients with active AS. It was conducted at 16 investigator sites in 4 countries (10 sites in USA, 4 centres in Germany, 2 sites in UK and 2 centres in the Netherlands) between March 2009 and May 2011. The primary objective of Part 1 of Study A2209 was to evaluate the efficacy of SEK after two IV doses of 10 mg/kg (given 3 weeks apart – baseline and week 3) compared to PBO based on the proportion of subjects achieving ASAS20 response at 6 weeks. The main objective of Part 2 was to evaluate the efficacy of lower doses of SEK (2 IV infusions, given 3 weeks apart) at 6 weeks based on the change from baseline in the total BASDAI score.

Study A2209 was conducted in 2 parts and consisted of 3 study periods for both parts. Firstly, a screening period of up to 4 weeks followed by an active treatment period of 3 weeks and then a post-treatment follow-up period of 25 weeks. At baseline in Part 1, eligible subjects (planned to be 30) were randomised to either IV SEK 10 mg/kg (2 infusions, given 3 weeks apart at baseline and week 3) or matching IV PBO infusions in a ratio of 4:1. In Part 2 of the study, a total of 30 patients were planned to be randomized in a ratio of 2:2:1 to IV SEK 0.1 mg/kg, SEK 1.0 mg/kg or SEK 10 mg/kg. All subjects were to receive 2 IV infusions, 3 weeks apart (baseline and week 3) in Part 2.

Subject assessments in both Parts 1 and 2 were scheduled to occur weekly for the first 4 weeks after baseline, then every 2 weeks until week 12 and then monthly thereafter up until week 28.

The trial protocol was amended 6 times, 3 of which occurred prior to patient enrolment. The first 3 amendments contained clarifications about efficacy assessments; inclusion, exclusion and early termination criteria; and study drug handling. Amendments 4 and 5 contained information relating to 4 interim data analyses. The last amendment introduced an alternative drug preparation plan as the lowest proposed dose of 0.1 mg/kg (in Part 2) had not undergone prior compatibility testing but was applicable to all 3 examined dose levels to ensure that blinding was preserved.

Study A2209E1

Patients who completed the core study period of Study A2209 were eligible to enter an open-label, non-randomized trial (Study A2209E1) in which all subjects were administered IV SEK 3 mg/kg every 4 weeks up until week 24 (Part 1) with a possible extension of an additional 6 months of therapy (Part 2). Study A2209E1 was conducted between April 2010 and December 2012. The primary objective of Study A2209E1 was to assess the safety and tolerability of continued SEK therapy; however, some efficacy outcomes were also collected as an exploratory objective.

Inclusion and exclusion criteria

Study A2209

To be eligible for inclusion in Study A2209 (either part), patients had to be aged between 18 and 65 years with a diagnosis of moderate to severe AS according to the modified New York criteria for AS. All subjects were required to have each of the following criteria representing active disease despite taking the maximal recommended dose of NSAID therapy (at least 1 drug) for a minimum of 3 months: back pain and nocturnal pain score $\geq$4 (on 10 point VAS) and BASDAI

score ≥4 (on 10 point scale). Elevation of serum inflammatory markers (ESR or CRP) was not required for entry into this trial.

Concomitant treatment with either MTX (up to 25 mg/week) or sulfasalazine was allowed in Study A2209 if the dose of therapy had been stable for at least 4 weeks prior to randomisation. Patients taking DMARDs other than MTX or sulfasalazine were required to cease such therapy for at least 4 weeks prior to randomisation (or 8 weeks if taking leflunomide and it is not removed by cholestyramine washout). The concomitant use of oral CS was permitted for subjects taking stable doses (prednisone [or equivalent] <10 mg/day) for at least 4 weeks prior to randomisation. No CS injections (intra-articular or parenteral) were permitted within 4 weeks of randomisation. Concomitant NSAID was also permitted, provided subjects were on a stable dose for at least 4 weeks prior to randomisation. Patients who had previously received anti-TNF therapy were allowed to be included as long as such therapy had been ceased 2-3 months prior to baseline.

Co-morbid conditions were an exclusion criterion based on investigator decision as to their clinical significance (including cardiac, pulmonary, neurologic, psychiatric and any major uncontrolled disease). A patient with a history of infection requiring treatment within 2 weeks of baseline, and a history of blood donation or loss of 400 mL of blood within 8 weeks prior to screening was to be excluded. A history of malignancy (except for excised basal cell skin cancers or cervical carcinoma in situ successfully treated) was also an exclusion criterion. Patients with active or history of clinically significant cardiac abnormalities such as left bundle branch block on ECG, atrial fibrillation, left ventricular dysfunction, symptomatic coronary artery disease or hospitalised in the preceding 6 months because of cardiac disease were also to be excluded.

Subjects were screened for Hepatitis B and C, HIV as well as latent TB at baseline. Subjects with active TB were excluded, but those with latent TB could be included after treatment according to local country guidelines was initiated. All patients were required to have a chest X-ray within 12 weeks prior to screening. Subjects with significant laboratory abnormalities at screening and baseline were excluded. This included serum transaminases >2 x ULN, total serum bilirubin >2 x ULN, total white blood cell count <4.5 x 10^9/L or >11 x 10^9/L and platelet count <100 x 10^9/L.

Study A2209E1

To be included into the open-label extension trial, subjects had to participate up to and complete the week 28 study visit assessments of the preceding study (A2209). If a patient had discontinued from Study A2209 after the week 16 visit because of unsatisfactory therapeutic effect, then they were eligible to enter into Study A2209E1 provided they did so within 3 weeks of withdrawal and meet the same criteria for defining active AS at baseline in Study A2209. All patients were re-tested for Hepatitis B and C virus, as well as HIV infection before commencing in Study A2209E1.

Study treatment, randomisation and blinding

Study A2209

In Part 1 of this trial, patients were randomised centrally in a ratio of 4:1 to IV SEK 2 x 10 mg/kg (2 infusions, 3 weeks apart on study days 1 and 22) or matching PBO infusions. In Part 2 of Study A2209, patients were randomised centrally in a ratio of 2:2:1 to IV SEK 2 x 0.1 mg/kg, IV SEK 2 x 1.0 mg/kg or SEK 2 x 10 mg/kg infusions. All subjects in Part 2 were scheduled to receive 2 IV infusions of SEK, given 3 weeks apart on study day 1 and 22. There was no PBO control arm in Part 2.

In both study parts, SEK was supplied in 50 mg lyophilised vials and reconstituted with 1.2 mL of sterile water. The SEK concentrate solution was diluted in 5% glucose bags for IV infusion through a 0.2 micron in-line filter. Patients were monitored for up to 4 hours after their first infusion of SEK. Study A2209 (Parts 1 and 2) was a double-blind trial with patients and investigators blinded to treatment allocation.

Study A2209E1

No randomisation or blinding was undertaken in Study A2209E1. All enrolling subjects were administered IV SEK 3 mg/kg every 4 weeks for 6-12 months in this open-label extension trial. In this trial, SEK was supplied in 50 mg lyophilised vials and reconstituted/infused in an identical manner to Study A2209.

Efficacy criteria

Study A2209

The primary efficacy outcome in Part 1 of Study A2209 was the comparative ASAS20 response rate at week 6 between SEK 10 mg/kg (2 IV infusions given 3 weeks apart) and PBO.

The primary efficacy outcome in Part 2 of Study A2209 was the mean change from baseline to week 6 in the total BASDAI score for the 2 lower doses of SEK (0.1 mg/kg and 1.0 mg/kg) compared to SEK 10 mg/kg therapy (using the combined data for patients receiving this dose of SEK in Parts 1 and 2).

There were a number of secondary and exploratory efficacy endpoints in Study A2209, the main outcomes being:

- ASAS20 response rate at other time points up to week 28,
- ASAS40, ASAS 5/6 and partial remission rates at each time point up until week 28,
- Change from baseline in BASDAI, BASFI and BASMI scores at each time point up to week 28,
- Change from baseline in CRP readings, and
- MRI response to treatment at 6 and 28 weeks of follow-up (Part 1 only).

Study A2209E1

The exploratory efficacy outcomes reported in this open-label, extension trial included the rates of ASAS20, ASAS40, ASAS 5/6 improvement and ASAS partial remission over time, as well as the mean change from baseline in BASDAI score and median CRP values up to week 52.

Statistical considerations and sample size

Study A2209

The primary efficacy analysis population in both parts of Study A2209 included all subjects who received at least 1 dose of study medication, had evaluable efficacy data and no significant protocol deviations that may have impacted upon their efficacy assessments. The primary efficacy outcome in Part 1 was a treatment comparison between SEK 10 mg/kg and PBO for rate of ASAS20 response at 6 weeks using a Bayesian model. A meta-analysis of 8 published AS trials was undertaken to quantify the historical PBO response rate (up to 11 potential responders out of a total of 43 PBO treated subjects) and generate a Beta distribution with the parameters lying between 0.5 and 1 (i.e. the prior probability Beta calculation ensured that SEK had a higher than 50% response rate compared with PBO). A binomial distribution was assumed for the trial's observed data with posterior distributions for the response rates being calculated.

In order to evaluate the efficacy of different doses of SEK in Part 2 of the study, a longitudinal linear mixed effect model was fitted for the change from baseline in BASDAI. Data from both parts of the trial were included in this analysis. Treatment group (SEK 0.1 mg/kg, SEK 1.0 mg/kg, SEK 10mg/kg or PBO), visit, study part (Part 1 or Part 2) and the interaction between treatment group and visit were included as factors. Baseline BASDAI was included as a covariate and the interaction between visit and baseline was estimated. An unstructured covariance matrix was used to model the correlation within subjects. From the model, the hypothesis that either of the 2 lower doses of SEK was better than SEK 10 mg/kg when tested at the unadjusted 1-sided 20% significance level was examined. Missing data was not imputed and no supportive statistical analyses were undertaken in either part of Study A2209.

The sample size calculations in Part 1 were based on the number of patients required to obtain a posterior probability of at least 95% that the ASAS20 response at 6 weeks with SEK treatment is superior to PBO. With 20 patients in the SEK arm and 5 in the PBO group, the study had at least 90% power to detect a statistically significant difference between the 2 treatment groups in the proportion of ASAS20 responders, assuming a response rate of 60% in the SEK treatment group and 25% in the PBO arm. The total sample size for Part 1 was increased by 5 subjects to allow for the estimated number of patient discontinuations and/or incomplete data.

With a sample size of 10 patients in at least 1 of the 2 lower SEK dose groups in Part 2, and 25 patients receiving SEK 10 mg/kg in total (Parts 1 and 2 combined), Study 2209 had ~77% power to detect a statistically significant difference between the 2 treatment groups for the change from baseline in BASDAI score, assuming a true treatment difference of 1.5 (SD 2.5) between the high and low dose SEK treatment groups (based on a 1–sided alpha level of 20%). The total sample size for Part 2 was increased by 5 subjects to allow for the estimated number of patient discontinuations and/or incomplete data.

Study A2209E1

Descriptive statistics were used to summarise efficacy variables over time and no inferential analyses of this data was performed. There was no sample size calculation for Study A2209E1.

Patient disposition and protocol deviations

Study A2209

A total of 30 subjects (24 in the SEK 10 mg/kg arm and 6 in the PBO group) were enrolled and randomised in Part 1 of Study A2209. Albeit small numbers, a higher percentage of subjects in the PBO group (50.0%; 3/6) compared to the SEK arm (33.3%; 8/24) discontinued before week 28. The 3 patients in the PBO group who withdrew, did so for 3 separate reasons (1 category each): withdrawal of consent, adverse event and unsatisfactory benefit. The 8 patients in the SEK group who prematurely discontinued from Part 1 did so because of consent withdrawal (n=3), unsatisfactory therapeutic effect (n=3) and singular cases of adverse event and lost to follow-up.

In Part 2 of Study A2209 (n=30 subjects in total), 2 of 6 patients treated with SEK 10 mg/kg prematurely discontinued – singular cases of consent withdrawal and unsatisfactory effect. In the SEK 1.0 mg/kg arm, 5 of 12 subjects (41.7%) prematurely discontinued before 28 weeks because of unsatisfactory therapeutic effect (n=3); and there were singular cases of lost to follow-up and administrative problems. In the SEK 0.1 mg/kg arm, 5 of 12 subjects (50%) prematurely discontinued before 28 weeks because of unsatisfactory therapeutic effect (n=5) and 1 case of lost to follow-up. Most of the discontinuing subjects withdrew after 6 weeks. Only 2 patients in the SEK 10 mg/kg group and 3 subjects in the PBO arm withdrew at or before 6 weeks in the study.

In both parts of Study A2209, several minor protocol deviations were recorded, but only 2 patients (1 in the SEK 10 mg/kg group and 1 in the SEK 0.1 mg/kg arm) were excluded from the primary efficacy analysis because of significant protocol deviations that may have impacted their results. The patient from the SEK 10 mg/kg group who was excluded from the efficacy analysis dataset had a baseline BASDAI score <4 and a positive TB test, both of which made the subject ineligible for enrolment. The patient in the SEK 0.1 mg/kg arm who was excluded received an intramuscular CS injection for elbow pain during the trial (i.e. they received prohibited concurrent treatment).

Study A2209E1

A total of 39 patients enrolled in this extension study from Study A2209: 21 previously received SEK 10 mg/kg, 8 previously received SEK 1.0 mg/kg, 7 previously received SEK 0.1 mg/kg and 3 were in the PBO arm. All 39 subjects received at least 1 dose of IV SEK 3 mg/kg in Study A2209E1 and had at least 1 evaluable post-baseline efficacy assessment. Despite a total of 40

minor protocol deviations affecting 24 subjects in Study A2209E1, none of the 39 enrolled patients were excluded from the efficacy analysis.

Most subjects (71.8%; 28/39) completed the extension phase. A total of 11 patients (8 in the prior SEK 10 mg/kg dose group) prematurely discontinued in Study A2209E1 due to the following reasons: 3 subjects because of serious adverse events, 3 patients due to lack of therapeutic benefit and 2 subjects each withdrew consent and experienced administrative problems plus 1 subject was lost to follow-up.

Baseline data

Study A2209 - Part 1 only

In Part 1 of the study, the 2 treatment groups were comparable for demographic characteristics. The majority of subjects enrolled in this trial were Caucasian (87%; 26/30) with a mean age of 42 years (range: 23-65 years). More than half (63%; 19/30) of all patients were male with a mean BMI of 26.7 kg/m^2 (range: 16-42 kg/m^2). The mean duration of AS was identical in both treatment groups at 10.1 years. The majority of subjects (72%; 21/30) had a positive HLA-B27 test and 14% (4/30) of subjects had co-existent skin psoriasis. More than half (55%; 16/30) of all subjects had peripheral arthritis in addition to axial disease, and almost one third (31%; 9/30) had a history of uveitis. In addition, 14% (4/30) had a history of inflammatory bowel disease.

In terms of AS disease activity at baseline, the mean BASDAI and BASMI scores were 7.1 and 4.3, respectively, in the SEK treatment group and 7.2 and 3.7, respectively, in the PBO arm. The mean baseline CRP readings were similar in both treatment groups at 13.2-13.3 mg/L. Only 4 subjects (all in the SEK group) were taking concomitant MTX at baseline and during the trial and 8 patients (5 in the SEK arm) were taking sulfasalazine. Overall, almost half of all subjects (45%; 10 in the SEK arm and 3 in the PBO group) had a history of prior exposure to anti-TNF therapy. Nearly all subjects (97%; 28/30) were taking concomitant NSAIDs in Part 1 of Study A2209. Moreover, 2 patients in the SEK treatment group were using systemic CS at baseline.

Study A2209 - Parts 1 and 2 combined

The demographic parameters for Parts 1 and 2 of Study A2209 combined were similar for the 4 treatment groups. The majority of subjects enrolled in this trial were Caucasian (92%; 55/60) with a mean age of 42.8 years (range: 23-65 years). More than half (63%; 38/60) of all patients were male with a mean BMI of 26.9 kg/m^2 (range: 16-42 kg/m^2). The mean duration of AS in the complete cohort was 9.9 years. About two thirds of all subjects (67%; 39/60) had a positive HLA-B27 test and 10% (6/60) of subjects had co-existent skin psoriasis. Just less than half (43%; 25/60) of all subjects had peripheral arthritis in addition to axial disease, and one quarter (26%; 15/60) had a history of uveitis. In addition, 10% (6/60) had a history of inflammatory bowel disease.

In terms of AS disease activity at baseline, the mean BASDAI and BASMI scores were similar between the 4 treatment groups at 7.1 and 4.1, respectively. The mean baseline CRP value for the entire cohort was 14.5 mg/L. Only 14% (8/60) of all subjects (4 in the SEK 10 mg/kg group and 2 subjects in each of the other 2 SEK arms) were taking concomitant MTX at baseline. In total, 13 patients (including 7 in the SEK 10 mg/kg arm) were taking sulfasalazine. Overall, almost half of all subjects (47%; 27/60) had a history of prior exposure to anti-TNF therapy. The majority of subjects (83%; 48/60) were taking concomitant NSAID and 4 patients (3 in the SEK 10 mg/kg treatment group and 1 in the SEK 0.1 mg/kg arm) were using systemic CS at baseline.

Study A2209E1

The 39 enrolled patients in this extension trial had a mean age of 42.5 years and most were of Caucasian ethnicity (90%; 35/39). The majority of subjects were male (59%; 23/39) with a mean BMI of 27.3 kg/m^2 (range: 15-43 kg/m^2). The baseline AS characteristics at the start of the

extension trial period included a mean BASDAI score of 6.1, mean BASMI score of 3.9, mean BASFI score of 6.0 and a mean baseline CRP value of 8.0 mg/L. Only 1 patient in Study A2209E1 had a history of prior anti-TNF exposure. Concurrent medication use in the extension trial was low with only 31% (12/39) of subjects taking NSAID, 10% (4/39) taking oral CS and 5% (2/39) taking MTX.

Efficacy results

Study A2209 – Part 1

The primary efficacy endpoint for Part 1 of Study A2209 was achieved with the rate of ASAS20 response at 6 weeks being 60.9% (14/23) in the SEK 10 mg/kg group compared to 16.7% (1/6) in the PBO arm. A Bayesian analysis of the 6-week ASAS20 response rates revealed a treatment related difference of 34.7% (95% CI 11.5%, 56.4%) with a 99.8% probability that SEK was superior to PBO in achieving this outcome.

At week 6, the rates of ASAS40, ASAS 5/6 improvement and ASAS partial remission were consistently numerically higher for those who received SEK compared to PBO: 30% (7/23) versus 17% (1/6) for ASAS40 response, 35% (8/23) versus 0 for ASAS 5/6 improvement and 9% (2/23) versus 0 for ASAS partial remission. Responses with SEK were seen as early as week 2. Between weeks 8 and 28, the response rates to SEK gradually declined for all of the ASAS composite parameters. For example, the ASAS20 response rate declined from 61% (8/23) at week 6 to 30% (7/23) at weeks 24 and 28. In general, the mean reductions from baseline in the BASDAI, BASFI and BASMI scores as well as CRP reductions reached a maximal level of response with SEK at 4-6 weeks, then plateaued or slightly deteriorated between weeks 8 and 24 in Part 1 of Study A2209. These observations are consistent with the PD activity of SEK.

A total of 27 patients (22 in the SEK 10 mg/kg group and 5 in the PBO arm) enrolled in Part 1 had evaluable MRI images of the spine and SI joints at baseline in Study A2209. There was a marked imbalance in MRI inflammatory scores at baseline: mean and median of 9.2 and 5.5, respectively, for SEK compared with 20.6 and 21, respectively, for PBO, which made it difficult to make between treatment comparisons in this small sub-study. At weeks 6 and 28, there was no significant change in MRI inflammatory scores for the PBO group (e.g. mean and median scores at week 28 of 19). At week 6, the mean MRI inflammatory score in the SEK treated group had reduced from 9.2 to 6.6 (with a stable mean of 5.5; n=22 subjects). Further reductions were observed in the SEK group at week 28 (n=16) with the mean MRI inflammatory score reducing further to 5.7 (median 2.5).

Study A2209 - Parts 1 and 2 combined

At week 6, the primary endpoint (mean change from baseline in BASDAI score) for Part 2 was not met. As summarised in Table 22, the pair-wise comparisons of each lower dose SEK (0.1 and 1.0 mg/kg) versus SEK 10 mg/kg using the model adjusted mean change from baseline in the BASDAI score was not statistically significant at the 1-sided 20% level. Using the unadjusted data, the LS mean change from baseline to 6 weeks was -1.9 points for the SEK 10 mg/kg group, -2.0 for the SEK 1.0 mg/kg arm, -1.2 for the SEK 0.1 mg/kg group and -1.1 for the PBO arm.

Table 22: Statistical Analysis of the Change from Baseline to 6 Weeks in BASDAI in Study A2209.

		Difference vs AIN457 10mg/kg		
Treatment group	Adjusted mean change from baseline	Estimate	95% CI	P-value*
AIN457 2x0.1mg/kg	-1.20	0.67	(-1.09 , 2.43)	0.22
AIN457 2x1.0mg/kg	-2.02	-0.14	(-1.85 , 1.56)	0.57
AIN457 2x10mg/kg	-1.87			

Although no formal statistical testing was undertaken, the various categories of ASAS response were numerically higher with SEK 10 mg/kg versus the 2 lower doses of SEK (in a dose related relationship). At week 6, the rates of ASAS20, ASAS40, ASAS 5/6 improvement and ASAS partial remission were consistently higher for those who received SEK 10 mg/kg compared to SEK 1.0 mg/kg and SEK 0.1 mg/kg, respectively: 59% (16/27) versus 36% (4/11) and 27% (3/11) for ASAS20 response rate, 30% (8/27) versus 18% (2/11) and 27% (3/11) for ASAS40 response rate, 32% (9/28) versus 27% (3/11) and 18% (2/11) for ASAS 5/6 improvement and 7% (2/28) versus 0 for both lower doses of SEK regarding the rate of ASAS partial remission.

Both the SEK 10 mg/kg and 1.0 mg/kg dose groups, but not the 0.1 mg/kg arm, showed clinically relevant mean reductions in CRP from baseline to week 6. In the SEK 10 mg/kg group, mean CRP reduced from 14.5 mg/L at baseline to 5.4 mg/L at week 6, and in the SEK 1.0 mg/kg arm mean CRP reduced from 22.2 mg/L to 13.4 mg/L. There was no significant change in mean CRP (7.5-7.7 mg/L) over 6 weeks for the SEK 0.1 mg/kg dose group. In the SEK 10 mg/kg and 1.0 mg/kg dose arms, mean CRP gradually rising again from week 8 or 10 until they returned to their baseline levels by week 20-24. All 3 SEK dose groups demonstrated 10-20% mean improvements in BASFI and BASMI scores between baseline and week 6 with no clinically significant numerical differences between the 3 SEK dose groups.

Study A2209E1

At 24 weeks of therapy in the extension trial, the following rates of ASAS response were observed: 50% (19/38) for ASAS20, 26% (10/38) for ASAS40, 34% (13/38) for ASAS 5/6 improvement and 5% (2/38) for ASAS partial remission. Clinical responses were generally maintained over 52 weeks of continued SEK therapy. The following rates of ASAS response were recorded at 52 weeks of continued therapy in Study A2209E1: 55% (21/38) for ASAS20, 42% (16/38) for ASAS40, 49% (19/39) for ASAS 5/6 improvement and 5% (2/39) for ASAS partial remission.

At 24 and 52 weeks of continued SEK therapy in Study A2209E1, the mean baseline BASDAI score was 4.5 (n=35) and 3.9 (n=31), respectively, which is a moderate reduction from the baseline value of 6.1 at the commencement of the extension trial. Median CRP levels rapidly declined from 8.0 mg/L at baseline to 3.6 mg/L on day 15, and stayed around 3.0 mg/L over the rest of the extension study period.

7.3.3. Analyses performed across trials (pooled & meta analyses)

The sponsor has provided an integrated data analysis of the AS studies consisting of tables and figures which pool the data for demography and other study population characteristics, exposure to study medication and efficacy endpoints. The principal aim of the pooled dataset was to examine for subgroup variables, such as subject age, gender and ethnicity; baseline subject weight categories and hsCRP (< 10 mg/L versus >10 mg/L); geographic region and prior anti-TNF use (yes/no) plus reason for stopping anti-TNF (primary or secondary efficacy failure or tolerability issue). The key findings from the pooled dataset were consistent with that

observed in the pivotal Phase 3 studies. In particular, the rates of ASAS20 and ASAS40 response at 16 weeks were lower in the anti-TNF experienced cohort (regardless of reason for anti-TNF failure) versus subjects who were anti-TNF naïve, and subjects weighing >90 kg had decreased levels of response to all treatments compared to patients weighing <90 kg. The only new finding from the pooled dataset was that patients with higher (>10 mg/L) baseline hsCRP levels had higher rates ASAS20 and ASAS40 response at week 16 to SEK compared to those with lower (≤10 mg/L) baseline hsCRP levels, although both hsCRP groups demonstrated better response rates with SEK than PBO.

7.4. Evaluator's conclusions on clinical efficacy for Indication 2

In support of the extension of treatment indication for SEK to include AS, this submission contains 2 pivotal Phase 3 studies (F2305 and F2310) of highly similar design, as well as 1 supportive Phase 2 trial (A2209) of 28 weeks duration, which enrolled a total of 60 patients (30 of whom received IV SEK 10 mg/kg). The Phase 2 trial also had an open-label extension period (A2209E1) of up to 52 weeks duration, which enrolled a total of 39 patients.

Both of the Phase 3 studies are ongoing with interim study reports up to 52 weeks of treatment follow-up being included in this submission. A total of 590 patients were enrolled in the 2 Phase 3 studies, of which 393 subjects received either dose of SEK (75 mg or 150 mg injections) in the first 16 weeks (i.e. the true PBO-controlled period). In both Phase 3 studies, ~20% of PBO treated patients at week 16 were considered responders and so continued on PBO up to week 24. At weeks 16 or 24, all continuing PBO treated subjects (90.8%; 178/196) were switched to either SEK 75 mg or 150 mg SC injections every 4 weeks in the maintenance treatment phase.[10] In total, >90% of subjects completed their week 16 assessment and ~85% of patients completed 52 weeks of treatment follow-up in the Phase 3 program.

Both of the Phase 3 studies were randomised, double-blinded and PBO-controlled in design and enrolled adult patients with a confirmed diagnosis of AS according to the modified New York criteria. Subjects were required to have moderate-severe disease activity at baseline with the BASDAI score being ≥4 and spinal pain ≥4 cm, despite at least 3 months of conventional treatment with NSAID and/or conventional DMARD (SSZ or MTX). The Phase 3 studies were highly similar in design with the main difference being the use of an IV loading dose of SEK in Study F2305 versus a SC loading dose strategy in Study F2310. Both of the Phase 3 trials examined the effect of 2 doses of SEK (75 mg and 150 mg injections, given every 4 weeks by SC injection in the maintenance treatment phase) compared to PBO. The baseline demographic and disease related characteristics of patients in the Phase 3 trials are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were male, of Caucasian ethnicity, and within the expected age range of 25- 65 years. Over one quarter of all recruited subjects were a current smoker, which is a factor associated with diminished response to treatment. However, there are some caveats to the generalisability of the treatment population. For example, both studies excluded patients who were at a significant risk of infection or malignancy, or who had various abnormal laboratory results at baseline (e.g. abnormal haematology or liver function tests). In addition, a history of inflammatory bowel disease and uveitis were exclusion criteria, and these conditions are co-morbidities in ~10% of the target population. At randomisation, patients were stratified on the basis of whether they were anti-TNF naïve or anti-TNF-IR. In total, 31.2% (184/590) of all subjects recruited into the Phase 3 AS program had a history of anti-TNF exposure.

This submission is seeking an indication in active AS and is generally consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EU guideline

[10] In Study F2310, all placebo patients were re-randomised at Week 16.

CPMP/EWP/4891/03 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis" (effective 23 February 2010). However, the Phase 3 trials did not evaluate anti-TNF drugs as the active comparator, which "may be required" according to the TGA adopted EU guideline. However, there is no precedent for the registration of a non-anti-TNF drug in AS and none of the 5 anti-TNF drugs currently registered for AS have conducted head-to-head studies with anti-TNF therapies. Furthermore, both of the Phase 3 SEK trials did include patients who had previously been exposed to anti-TNF drugs and those who were anti-TNF naive. For both Phase 3 studies, the choice of efficacy endpoints and statistical analysis were appropriately performed; and strategies to maintain blinding and randomisation procedures were suitable.

The primary efficacy endpoint in both Phase 3 studies was the rate of ASAS20 response at week 16. The pre-specified secondary efficacy endpoints (all evaluated at week 16) included various other levels of ASAS response (ASAS40, ASAS 5/6 improvement and ASAS partial remission) as well as the change from baseline in hsCRP levels and the total BASDAI score; and health related QOL measures, notably the LS mean change from baseline in the SF-36 PCS and ASQoL scores. Study F2305 also included an analysis of MRI data of the SI joints in a subset of anti-TNF-naïve patients (n=105 subjects). Both the Phase 3 studies also provided some efficacy data up to week 52 in support of the maintenance of treatment effect.

In Study F2305, where IV loading with SEK 10 mg/kg at baseline, week 2 and week 4 was given to both SEK treatment groups, the primary efficacy endpoint of a statistically superior ASAS20 response at 16 weeks was reached with both doses of SEK. Overall, 59.7% (74/124) of patients treated with SC SEK 75 mg every 4 weeks in the maintenance phase and 60.8% (76/125) of subjects treated with SC SEK 150 mg injections achieved this outcome versus 28.7% (25/122) of patients in the PBO group. Many secondary efficacy measures of clinical relevance such as various rates of ASAS response (40, 5/6 improvement and partial remission) at 16 weeks, as well as mean change from baseline in the BASDAI score confirmed that SEK is effective in treating the symptoms and signs of active AS. Improvements in measures of inflammation (CRP), imaging (MRI parameters), physical functioning (BASFI), spinal mobility (BASMI), and health related QOL were also beneficially attained with SEK therapy. There were no significant differences at 16 weeks between the 2 SEK dosing regimens in Study F2305, but this probably reflects the impact of the high dose IV loading regimen in the first 4 weeks of the trial with efficacy endpoint analysis being primarily conducted at week 16.

In contrast, Study F2310 (i.e. where no IV loading dose regimen was included) showed only treatment with SEK 150 mg SC every 4 weeks showed superiority over PBO at week 16 in the primary and ranked secondary endpoints (apart from ASAS partial remission rate) in the hierarchical testing strategy that controls for multiplicity of testing with adjusted p-values. In Study F2310, treatment with SEK 75 mg SC every 4 weeks was not superior to PBO for any efficacy endpoint (primary or secondary) in the testing hierarchy. Furthermore, SEK 75 mg SC injection every 4 weeks demonstrated clinically lower absolute response rates compared to the SEK 150 mg dose arm for all efficacy endpoints at week 16.

Overall, SEK 150 mg therapy given by SC loading (as observed in Study F2310) had a similar magnitude of efficacy for the primary and secondary endpoints compared to the IV SEK loading regimens examined in Study F2305, indicating the optimal response to SEK is achieved with the proposed 150 mg SC dosing posology (every 4 weeks in the maintenance phase) and no additional benefit with SEK was observed with IV loading.

The Phase 3 study data also shows that SEK 150 mg by SC injection every 4 weeks is effective in treating both anti-TNF naïve as well as anti-TNF-IR patients. However, in both Phase 3 trials ASAS20 response rates at week 16 were numerically higher in anti-TNF naïve subjects (66-68%) compared with anti-TNF-IR patients (45-50%). Although not stratified for at randomisation, high subject weight at baseline (>90 kg versus $\leq$90 kg) also appeared to be associated with lower ASAS response rates for SEK 150 mg treatment.

The efficacy data available at 52 weeks in both Phase 3 studies indicated that the majority of responding patients appear to maintain their treatment related benefit with continued SEK up to 52 weeks of follow-up. In addition, for PBO patients who switched to SEK at week 16 or 24, the rate of ASAS responses observed at 52 weeks (i.e. 24-32 weeks after switching to active treatment) were similar to those achieved in the originally treated SEK cohort.

The supporting Phase 2 Study A2209 showed that treatment with 2 IV doses of SEK 10 mg/kg (3 weeks apart) was superior to PBO for the rate of ASAS20 response at week 6 (60.9% [14/23] for SEK versus 16.7% [1/6] for PBO). Various secondary clinical efficacy outcomes and MRI data supported the benefit of SEK over PBO in this proof-of-concept trial. The study also contained a dose finding analysis for SEK (Part 2), which showed that the various categories of ASAS response were numerically higher for IV SEK 10 mg/kg versus the 2 lower doses of SEK (1.0 mg/kg and 0.1 mg/kg). Like the Phase 3 studies, the extension phase of this trial (A2209E1) showed that clinical efficacy was maintained in the majority of subjects up to 52 weeks with continued SEK therapy.

Overall, the data in this submission supports the efficacy of SEK therapy in the treatment of AS (diagnosed as per the 1984 modified New York criteria), in those with moderate-severely active disease at baseline, with or without concurrent NSAID or conventional DMARD (MTX or SSZ). SEK 150 mg by SC injection (given weekly for the first 4 weeks and then every 4 weeks thereafter) is the optimal dosing regimen in adult patients with AS. The requested dose of SEK therapy has demonstrated clinically meaningful efficacy in both anti-TNF naïve and anti-TNF-IR subjects. In the anti-TNF naïve group of patients, the magnitude of response with SEK is similar to that observed in the pivotal studies, which supported the registration of anti-TNF therapies in AS. Treatment related differences between SEK and PBO are 33% for the ASAS20 response rate (compared with 33% for anti-TNF therapy versus PBO) and 25% for the ASAS40 response rate (compared with 30% for anti-TNF therapy versus PBO).

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies for both treatment indications (Studies F2306 and F2312 for PsA and Studies F2305 and F2310 for AS), the following safety data were collected:

- Adverse Events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed weekly for the first 4 weeks, every 4 weeks between week 4 and 52, and then every 8 weeks thereafter.
- AEs of particular interest, including hypersensitivity reactions, infections (overall and serious), Major Adverse Cardiovascular Events (MACE), malignancy and the occurrence of inflammatory bowel disease were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, clinical chemistry and urinalysis were performed at baseline, weekly for the first 4 weeks, every 4 weeks until week 32 and then every 8 weeks thereafter. A fasting lipid profile was collected at baseline, every 8 weeks until week 24 and then at week 52, 76 and 104. Episodes of neutropenia were an AE of special interest as this was an identified risk with SEK.

- Screening tests for tuberculosis (Chest X-ray and QuantiFERON Gold testing; or PPD skin testing in countries without QuantiFeron Gold testing) were taken at baseline, but not routinely collected thereafter.
- Vital signs such as blood pressure, heart rate and temperature were performed at each scheduled study visit. Subject weight was assessed at baseline, week 24 and week 52.
- ECG for central reading was taken at baseline, week 16 and week 52.
- Urine pregnancy testing was performed at baseline and every 4 weeks thereafter in women of reproductive age.
- Serum for Anti-drug antibodies (ADA) to SEK was collected at baseline, week 24 and week 52.

In all 4 of the Phase 3 studies (2 for each treatment indication), the focus of the safety data presentation was on the true PBO-controlled period up to week 16 because this allowed a direct comparison across the randomized SEK treatment groups as well as the PBO arm prior to early escape for insufficient response. For both PsA and AS, the safety data from the Phase 3 studies was pooled for each treatment indication. In addition, for each of the treatment indications, the Phase 3 safety data was presented as analyses of information collected over the entire treatment period (i.e. as of the data cut-off date for the interim clinical study report). When comparing the rates of AEs after week 16 in both treatment indications, the interpretation of the findings is clouded as all PBO-treated subjects were switched to SEK therapy due to either early escape criteria at week 16 or a mandatory crossover at week 24. As such, the number of subjects as well as lengths of treatment follow-up differed between the different SEK dose groups for the entire treatment period. The safety data was primarily presented over the entire treatment period as an exposure adjusted incidence rate. For the PsA indication only, patient exposure over the entire treatment period in the 2 pivotal Phase 3 PsA studies was combined with that obtained in subjects with concomitant PsA who were involved in the Phase 3 PSOR trials. This appropriately expanded the safety dataset in the PsA indication.

AEs were summarised by the MedDRA classification using System Organ Class (SOC) and Preferred Term (PT) nomenclature.

8.1.2. Pivotal studies that assessed safety as a primary outcome

No pivotal studies in either the PsA and AS treatment indications program for SEK assessed safety as the primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The submission contained a single supporting Phase 2, dose-finding study for each treatment indication (Study A2206 for PsA [24 weeks duration] and Study A2209 for AS [28 weeks duration]). Both of the Phase 2 trials had open-label extension periods of up to an additional 52 weeks of treatment (Study A2206E1 for PsA and Study A2209E1 for AS) which also provided safety data on general AEs, AEs of special interest (e.g. infections), blood parameters (haematology and clinical chemistry), physical examination and anti-drug antibodies. The study reports from these supporting trials will be included in the overall SEK safety dataset in this clinical evaluation report.

8.1.4. Other studies evaluable for safety only

In addition, to the Phase 2 and 3 studies conducted in adult patients with PsA and AS, the submission contained safety data from the following 35 trials (listed by treatment indication) in support of the overall safety of SEK:

- PSOR – 11 completed trials (A2102, A2103, A2204, A2211, A2212, A2220, A2225, A2302, A2303, A2304 and A2307) plus 7 ongoing trials (A2211E1, A2223, A2302E1, A2304E1, A2308, A2309, and A2317),

- Rheumatoid Arthritis – 4 completed trials (A2101, F2201, F2206 and F2208),
- Multiple Sclerosis – 2 completed trials (B2201 and B2203),
- Crohn's Disease – 2 completed trials (A2202 and A2202E1),
- Uveitis – 2 completed trials (A2208 and C2303) plus 5 early termination studies (C2301, C2301E1, C2302, C2302E1 and C2303E1),
- Dry Eye Syndrome - 1 completed trial (CPJMR0092202) and
- Polymyalgia Rheumatica – 1 Proof-of-Concept, Phase 2 study (CPJMR0012201).

8.2. Pivotal studies that assessed safety as a primary outcome

This section is not applicable as no study in the PsA or AS clinical development programs for SEK assessed safety as the primary outcome.

8.3. Patient exposure

8.3.1. Psoriatic arthritis

8.3.1.1. Short term period (16 weeks) of phase 3 studies

The total patient exposure in the first 16 weeks (i.e. true PBO controlled period) of the 2 pivotal Phase 3 trials in PsA is summarised in Table 23. All of the 6 treatment groups (5 SEK dose groups and a PBO arm) had an identical median duration of patient exposure (112 days) to study medication. More than three quarters of all subjects (79.2% [557/703] in the pooled SEK cohort and 72.3% [217/300] in the PBO arm) were exposed to study treatment for at least 16 weeks.

Table 23: Duration of Exposure to Study Treatment (up to 16 Weeks) in Phase 3 PsA Trials.

Duration of exposure	AIN457 75mg N=99 n (%)	AIN457 150mg N=100 n (%)	AIN457 300mg N=100 n (%)	AIN457 10mg/kg -75mg N=202 n (%)	AIN457 10mg/kg -150mg N=202 n (%)	Any AIN457 dose N=703 n (%)	Placebo N=300 n (%)
Any exposure	99 (100)	100 (100)	100 (100)	202 (100)	202 (100)	703 (100)	300 (100)
>= 1 week	99 (100)	100 (100)	100 (100)	202 (100)	202 (100)	703 (100)	300 (100)
>= 4 weeks	99 (100)	100 (100)	98 (98.0)	199 (98.5)	202 (100)	698 (99.3)	300 (100)
>= 8 weeks	97 (98.0)	100 (100)	98 (98.0)	198 (98.0)	200 (99.0)	693 (98.6)	293 (97.7)
>= 12 weeks	95 (96.0)	100 (100)	97 (97.0)	195 (96.5)	198 (98.0)	685 (97.4)	283 (94.3)
>= 16 weeks	79 (79.8)	84 (84.0)	82 (82.0)	167 (82.7)	145 (71.8)	557 (79.2)	217 (72.3)
Days							
n	99	100	100	202	202	703	300
Mean	109.9	112.9	110.2	112.3	113.0	112.0	110.1
SD	13.34	4.13	15.37	15.55	16.08	14.33	15.10
Median	112.0	112.0	112.0	112.0	112.0	112.0	112.0
Min - Max	29 - 123	105 - 140	8 - 126	8 - 147	29 - 226	8 - 226	28 - 156
Patient-time (patient years)	29.8	30.9	30.2	62.1	62.5	215.5	90.4

Compliance with the study protocols was high as the vast majority of SEK treated subjects received all 7 doses of SC therapy by week 16 in Study F2312 and the same was true in Study F2306 where >95% of SEK treated patients received all 3 IV infusions plus 2 SC injections by

week 16. The overall cumulative exposure to SEK was 215.5 PY and for the PBO group it was 90.4 PY.

8.3.1.2. Entire treatment period of phase 3 studies

Patient exposure over the entire treatment period in the 2 pivotal Phase 3 PsA studies as well in those subjects with concomitant PsA who were involved in the Phase 3 PSOR trials is summarised in Table 24. The median duration of exposure to SEK was highest in the SEK 75 mg dose group at 413 days and this cohort was only represented by subjects who were involved in the 2 pivotal Phase PsA studies (i.e. no additional subjects from the PSOR trials were included in this dose group). The majority of subjects in the SEK 150 mg (64.3%; 438/681) were involved in the 2 Phase 3 PsA studies, but the converse was true for the SEK 300 mg dose group (63.4% [255/400] were enrolled in the Phase 3 PSOR trials). The expanded PsA population provides a large pool of safety across the 3 SEK doses of interest in this submission. The total cumulative exposure to SEK 75 mg therapy was 420.0 PY (all from the 2 Phase 3 PsA studies), 616.5 PY for SEK 150 mg injections (444.9 PY from the 2 Phase 3 PsA studies) and 278.6 PY for SEK 300 mg therapy (90.1 PY from the 2 Phase 3 PsA trials). In the 2 pivotal Phase 3 PsA studies, the vast majority of enrolled subjects received all doses of study treatment up to week 52 (17 injections in Study F2312 and 12 injections in Study F2306).

Table 24: Duration of Exposure to Study Treatment in Phase 3 PsA Trials as well as Subjects with concomitant PsA enrolled in Phase 3 Psoriasis Studies.

Duration of exposure	Any AIN457 75mg N=391 n (%)	Any AIN457 150mg N=681 n (%)	Any AIN457 300mg N=400 n (%)	Any AIN457 dose N=1472 n (%)	Placebo N=416 n (%)
Any exposure	391 (100)	681 (100)	400 (100)	1472 (100)	416 (100)
>= 1 week	391 (100)	681 (100)	400 (100)	1472 (100)	416 (100)
>= 4 weeks	388 (99.2)	681 (100)	397 (99.3)	1466 (99.6)	413 (99.3)
>= 8 weeks	382 (97.7)	671 (98.5)	394 (98.5)	1447 (98.3)	401 (96.4)
>= 12 weeks	376 (96.2)	653 (95.9)	373 (93.3)	1402 (95.2)	360 (86.5)
>= 16 weeks	373 (95.4)	581 (85.3)	323 (80.8)	1277 (86.8)	242 (58.2)
>= 20 weeks	371 (94.9)	570 (83.7)	306 (76.5)	1247 (84.7)	107 (25.7)
>= 24 weeks	367 (93.9)	556 (81.6)	298 (74.5)	1221 (82.9)	90 (21.6)
>= 52 weeks	225 (57.5)	317 (46.5)	101 (25.3)	643 (43.7)	4 (1.0)
>= 76 weeks	76 (19.4)	82 (12.0)	0	158 (10.7)	0
>= 100 weeks	2 (0.5)	4 (0.6)	0	6 (0.4)	0
Days					
n	391	681	400	1472	416
Mean	392.4	330.7	254.4	326.3	119.0
SD	151.10	158.89	108.28	153.23	46.31
Median	413.0	358.0	280.0	337.0	112.0
Min - Max	8 - 714	29 - 721	8 - 408	8 - 721	8 - 369
Patient-time (patient years)	420.0	616.5	278.6	1315.1	135.5

8.3.2. Ankylosing spondylitis

8.3.2.1. Short term period (16 weeks) of phase 3 studies

The total patient exposure in the first 16 weeks (i.e. true PBO controlled period) of the 2 pivotal Phase 3 trials in AS is summarised in Table 25. All of the 5 treatment groups (4 SEK treatment groups and the PBO arm) had a near identical median duration of patient exposure (112-113 days) to study medication. More than three quarters of all subjects (78.7% [310/394] in the pooled SEK cohort and 74.0% [145/196] in the PBO arm) were exposed to study treatment for at least 16 weeks.

Table 25: Duration of Exposure to Study Treatment (up to 16 Weeks) in Phase 3 AS Trials.

Duration of exposure	AIN457 75mg N=73 n (%)	AIN457 150mg N=72 n (%)	AIN457 10mg/kg -75mg N=124 n (%)	AIN457 10mg/kg -150mg N=125 n (%)	Any AIN457 N=394 n (%)	Placebo N=196 n (%)
Any exposure	73 (100)	72 (100)	124 (100)	125 (100)	394 (100)	196 (100)
>= 1 week	73 (100)	72 (100)	124 (100)	125 (100)	394 (100)	195 (99.5)
>= 2 weeks	73 (100)	72 (100)	123 (99.2)	125 (100)	393 (99.7)	195 (99.5)
>= 3 weeks	72 (98.6)	72 (100)	123 (99.2)	125 (100)	392 (99.5)	193 (98.5)
>= 4 weeks	72 (98.6)	72 (100)	123 (99.2)	125 (100)	392 (99.5)	192 (98.0)
>= 8 weeks	70 (95.9)	71 (98.6)	123 (99.2)	124 (99.2)	388 (98.5)	185 (94.4)
>= 12 weeks	69 (94.5)	68 (94.4)	121 (97.6)	124 (99.2)	382 (97.0)	181 (92.3)
>= 16 weeks	58 (79.5)	53 (73.6)	100 (80.6)	99 (79.2)	310 (78.7)	145 (74.0)
Days						
N	73	72	124	125	394	196
Mean	110.4	109.7	112.7	113.7	112.1	108.6
SD	19.29	11.34	15.38	10.75	14.30	22.54
Median	112.0	112.0	112.0	113.0	112.0	112.0
Min – Max	17-140	50-121	8-195	34-183	8-195	1-176
Subject-time (subject years)	22.1	21.6	38.3	38.9	120.9	58.3

Compliance with the study protocols was high as the vast majority of SEK treated subjects received all 8 doses of SC therapy by week 16 in Study F2310 and the same was true in Study F2305 where >95% of SEK treated patients received all 3 IV infusions plus 2 SC injections by week 16. The overall cumulative exposure to SEK was 120.9 PY and for the PBO group it was 58.3 PY.

8.3.2.2. Entire treatment period of phase 3 studies

Patient exposure over the entire treatment period in the 2 pivotal Phase 3 AS studies is summarised in Table 26. The median duration of exposure to SEK was comparable between the SEK 75 mg and 150 mg groups at 462-468.5 days. The majority of continuing subjects in both dose groups received all doses of study treatment up to week 52 (17 injections in Study F2310 and 12 injections in Study F2305) resulting in a similar cumulative exposure to SEK for both active dose groups (344.6-346.5 PY).

Table 26: Duration of Exposure to Study Treatment in Phase 3 AS Trials.

Duration of exposure	Any AIN457 75mg N=284 n (%)	Any AIN457 150mg N=287 n (%)	Any AIN457 N=571 n (%)	Placebo N=196 n (%)
Any exposure	284 (100)	287 (100)	571 (100)	196 (100)
>= 1 week	284 (100)	287 (100)	571 (100)	195 (99.5)
>= 4 weeks	282 (99.3)	286 (99.7)	568 (99.5)	192 (98.0)
>= 8 weeks	279 (98.2)	284 (99.0)	563 (98.6)	185 (94.4)
>= 12 weeks	273 (96.1)	280 (97.6)	553 (96.8)	181 (92.3)
>= 16 weeks	269 (94.7)	276 (96.2)	545 (95.4)	150 (76.5)
>= 24 weeks	266 (93.7)	269 (93.7)	535 (93.7)	28 (14.3)
>= 52 weeks	223 (78.5)	221 (77.0)	444 (77.8)	0
>= 76 weeks	80 (28.2)	78 (27.2)	158 (27.7)	0
>= 100 weeks	2 (0.7)	3 (1.0)	5 (0.9)	0
Days				
n	284	287	571	196
Mean	443.2	441.0	442.1	118.5
SD	144.82	141.06	142.82	32.83
Median	468.5	462.0	463.0	113.0
Min – Max	8-757	16-729	8-757	1-206
Subject-time (subject years)	344.6	346.5	691.1	63.6

8.3.2.3. All SEK treatment data pool

The sponsor has pooled and presented the safety data for all SEK treated subjects from a total of 42 Phase 1-3 clinical studies conducted in adult patients with various autoimmune conditions, for which either an interim or final clinical study report is available. The data pooling maximises the opportunity to observe rare but clinically significant AEs such as Major Adverse Cardiovascular Events (MACE) and malignancy by examining a large volume of data in patients exposed to SEK. Excluded from this large safety dataset are the 6 small trials (A1101, A2104, A2106, A2107, A2224 and A2228) that enrolled healthy volunteers. In addition, to the Phase 2 and 3 studies for PsA (n=4) and AS (n=4), the following trials (listed by treatment indication) were included in this overall safety dataset:

- PSOR – 11 completed trials (A2102, A2103, A2204, A2211, A2212, A2220, A2225, A2302, A2303, A2304 and A2307) plus 7 ongoing trials (A2211E1, A2223, A2302E1, A2304E1, A2308, A2309, and A2317),
- Rheumatoid Arthritis – 4 completed trials (A2101, F2201, F2206 and F2208),
- Multiple Sclerosis – 2 completed trials (B2201 and B2203),
- Crohn's Disease – 2 completed trials (A2202 and A2202E1),
- Uveitis – 2 completed trials (A2208 and C2303) plus 5 early termination studies (C2301, C2301E1, C2302, C2302E1 and C2303E1),
- Dry Eye Syndrome - 1 completed trial (CPJMR0092202) and
- Polymyalgia Rheumatica – 1 Proof-of-Concept, Phase 2 study (CPJMR0012201).

In total, 6200 subjects received at least 1 dose of SEK in the overall safety dataset with a cumulative exposure of 6267 PY, in a number of different autoimmune diseases – refer to Table 27. The median duration of exposure to SEK in the data pool was 370 days, with 5287 subjects being exposed to SEK for at least 16 weeks and 3671 patients for at least 52 weeks. Because most of the contributing studies in other autoimmune conditions enrolled fewer PBO treated subjects (as per their design), a significantly shorter duration of exposure was observed in the PBO cohort at 86 days, with a lower total cumulative exposure of 515.5 PY.

Table 27: Duration of Exposure to Treatment in All SEK Clinical Trials.

Duration of exposure	Any AIN457 dose N=6200	Placebo N=1665
Any exposure	6200 (100.00)	1665 (100.00)
>= 1 week	6192 (99.87)	1663 (99.88)
>= 4 weeks	6139 (99.02)	1640 (98.50)
>= 8 weeks	6031 (97.27)	1591 (95.56)
>= 12 weeks	5886 (94.94)	1385 (83.18)
>= 16 weeks	5287 (85.27)	631 (37.90)
>= 20 weeks	5049 (81.44)	321 (19.28)
>= 24 weeks	4964 (80.06)	247 (14.83)
>= 32 weeks	4699 (75.79)	86 (5.17)
>= 52 weeks	3671 (59.21)	34 (2.04)
>= 76 weeks	1137 (18.34)	2 (0.12)
>= 100 weeks	192 (3.10)	1 (0.06)
>= 132 weeks	108 (1.74)	0 (0.00)
>= 212 weeks	1 (0.02)	0 (0.00)
Days		
N	6200	1665
Mean	369.2	113.1
SD	202.44	63.71
Median	370.0	86.0
Min – Max	1 – 1548	1 – 752
Patient-time (patient-years)	6266.6	515.5

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

Psoriatic arthritis

Short Term Period (16 weeks) of Phase 3 Studies

The overall incidence of AEs up to week 16 was similar for the SEK 150 mg (57.0%; 57/100) and 300 mg SC dose groups (56.0%; 56/100) but lower for the SEK 75 mg SC therapy (48.5%; 48/99) compared to PBO (58.3%; 175/300). At 16 weeks, the frequency of AEs was slightly higher in the 2 SEK dose with IV loading at 60.4% (122/202) in the SEK 10 mg/kg-75 mg arm and 64.9% (131/202) in the SEK 10 mg/kg-150 mg group. The 16-week rate of AEs in the pooled SEK dataset was 58.9% (414/703). For the majority of SOC types, the incidence of AEs up to week 16 was similar between the 5 SEK dose groups and PBO apart from a higher overall rate of infectious AEs in the SEK treatment groups (29.2%; 205/703) versus PBO (25.7%; 77/300). This result was primarily explained by the higher frequency of infections in the SEK 10 mg/kg-150 mg arm (34.2%; 69/202) and to a lesser extent by infectious AEs in the SEK 150 mg SC dose group (30.0%; 30/100). The only other SOC with a higher incidence in the pooled SEK cohort (5.1%; 36/703) versus PBO (3.7%; 11/300) was abnormal investigations –refer to Table 28.

Table 28: Short Term Adverse Events by SOC in the Phase 3 Psoriatic Arthritis Studies.

Primary system organ class	AIN457 75mg N=99 n (%)	AIN457 150mg N=100 n (%)	AIN457 300mg N=100 n (%)	AIN457 10mg/kg -75mg N=202 n (%)	AIN457 10mg/kg -150mg N=202 n (%)	Any AIN457 dose N=703 n (%)	Placebo N=300 n (%)
- Any AE	48 (48.5)	57 (57.0)	56 (56.0)	122 (60.4)	131 (64.9)	414 (58.9)	175 (58.3)
Infections and infestations	23 (23.2)	30 (30.0)	29 (29.0)	54 (26.7)	69 (34.2)	205 (29.2)	77 (25.7)
Gastrointestinal disorders	11 (11.1)	17 (17.0)	12 (12.0)	27 (13.4)	20 (9.9)	87 (12.4)	35 (11.7)
Nervous system disorders	7 (7.1)	10 (10.0)	11 (11.0)	19 (9.4)	21 (10.4)	68 (9.7)	26 (8.7)
Skin and subcutaneous tissue disorders	5 (5.1)	6 (6.0)	8 (8.0)	20 (9.9)	20 (9.9)	59 (8.4)	29 (9.7)
Musculoskeletal and connective tissue disorders	7 (7.1)	8 (8.0)	6 (6.0)	18 (8.9)	14 (6.9)	53 (7.5)	40 (13.3)
General disorders and administration site conditions	14 (14.1)	5 (5.0)	5 (5.0)	15 (7.4)	13 (6.4)	52 (7.4)	21 (7.0)
Injury, poisoning and procedural complications	5 (5.1)	10 (10.0)	6 (6.0)	10 (5.0)	16 (7.9)	47 (6.7)	13 (4.3)
Metabolism and nutrition disorders	4 (4.0)	6 (6.0)	3 (3.0)	14 (6.9)	16 (7.9)	43 (6.1)	24 (8.0)
Investigations	3 (3.0)	2 (2.0)	6 (6.0)	12 (5.9)	13 (6.4)	36 (5.1)	11 (3.7)
Respiratory, thoracic and mediastinal disorders	2 (2.0)	3 (3.0)	6 (6.0)	11 (5.4)	11 (5.4)	33 (4.7)	26 (8.7)
Renal and urinary disorders	3 (3.0)	4 (4.0)	5 (5.0)	4 (2.0)	2 (1.0)	18 (2.6)	8 (2.7)
Vascular disorders	0	1 (1.0)	3 (3.0)	9 (4.5)	5 (2.5)	18 (2.6)	11 (3.7)
Blood and lymphatic system disorders	1 (1.0)	2 (2.0)	1 (1.0)	8 (4.0)	4 (2.0)	16 (2.3)	16 (5.3)
Psychiatric disorders	0	2 (2.0)	3 (3.0)	7 (3.5)	4 (2.0)	16 (2.3)	18 (6.0)
Cardiac disorders	2 (2.0)	1 (1.0)	3 (3.0)	4 (2.0)	5 (2.5)	15 (2.1)	9 (3.0)
Eye disorders	0	1 (1.0)	2 (2.0)	5 (2.5)	5 (2.5)	13 (1.8)	3 (1.0)
Reproductive system and breast disorders	1 (1.0)	0	2 (2.0)	3 (1.5)	4 (2.0)	10 (1.4)	3 (1.0)
Hepatobiliary disorders	0	2 (2.0)	1 (1.0)	2 (1.0)	3 (1.5)	8 (1.1)	2 (0.7)
Ear and labyrinth disorders	1 (1.0)	0	1 (1.0)	3 (1.5)	1 (0.5)	6 (0.9)	1 (0.3)
Immune system disorders	0	1 (1.0)	0	0	4 (2.0)	5 (0.7)	3 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.0)	0	0	1 (0.5)	1 (0.5)	4 (0.6)	1 (0.3)
Endocrine disorders	1 (1.0)	0	0	1 (0.5)	0	2 (0.3)	0

Primary system organ classes are sorted in descending order of frequency in Any AIN457 group.

The 4 most frequent individual types of AEs by PT (incidence ≥2.0% in the pooled SEK population) in the Phase 3 PsA studies up to week 16 were: nasopharyngitis (7.0% [49/703] in the pooled SEK cohort versus 5.7% [17/300] in the PBO group), Upper Respiratory Tract Infection (URTI; 6.3% [44/703] in the pooled SEK group versus 5.7% [17/300] in the PBO arm), headache (5.0% [35/703] in the pooled SEK cohort versus 3.3% [10/300] in the PBO group) and nausea (2.8% [20/703] in the pooled SEK group versus 2.0% [6/300] in the PBO arm). All 4 of the most common AEs by PT were more common in the SEK treatment population versus PBO, but their frequency was not dose dependent with SEK. None of other common types of AEs by PT (≥2.0% in any 1 treatment group) were more common (i.e. ≥1.0% difference in incidence) in the pooled SEK treatment population compared to PBO.

The most common types of infection by PT were URTI and nasopharyngitis, which occurred at a similar frequency in all SC SEK dose groups (75 mg, 150 mg and 300 mg). However, both IV dose regimens (15.3% in the SEK 75 mg maintenance group and 19.3% in the SEK 10 mg/kg-150 mg arm showed a higher overall incidence of both URTI and nasopharyngitis. Five patients, all treated with SEK (spread across the dose arms except nil in the 75 mg SC group) developed Candida infection (3 were oral, one was oesophageal [SEK 300 mg arm] and the other was

vulvovaginal in location) in the first 16 weeks of therapy. All cases were rated mild or moderate in severity and did not lead to treatment discontinuation. Herpes viral infections were more common in the SEK 300 mg group (5.0%) versus any other SEK dose arm (1.0% for all) and zero cases in the PBO group. The majority of herpes infections were oral in location. No herpes infections resulted in treatment discontinuation. No other opportunistic infections such as reactivation of latent TB or systemic fungal infection were experienced in the short term of either Phase 3 Study.

The overall AE profile between weeks 0 and 8 versus between weeks 8 and 16 (to examine for a potential effect of the SEK loading regimen) did not demonstrate any significant differences in the incidence and type of AEs by treatment period.

Entire treatment period of phase 3 studies

Over the entire treatment period, the exposure-adjusted incidence of AEs was comparable between the SEK 150 mg group (232.6 AEs per 100 PY; 342 AEs/147 PY) and the SEK 300 mg dose arm (222.3 AEs per 100 PY; 94 AEs/42.3 PY), but was lower in the SEK 75 mg group (186.5 AEs per 100 PY; 296 AEs/158.7 PY). Similar to the week 16 data, the 2 most common types of AEs by SOC (excluding musculoskeletal disorders, which partially reflects sub-optimal treatment rather than true AEs) over the entire treatment period were infections (81.7 AEs per 100 PY; 491 AEs/601.2 PY in the pooled SEK cohort) followed by gastrointestinal disorders (26.7 AEs per 100 PY; 215 AEs/805.5 PY). The exposure-adjusted incidence of infection showed a SEK dose response relationship occurring at a frequency of 71.9 AEs per 100 PY (198 AEs/275.4 PY) in the SEK 75 mg group, 88.7 AEs per 100 PY (233 AEs/262.7 PY) in the SEK 150 mg arm and 95.1 AEs per 100 PY (60 AEs/63.1 PY) in the SEK 300 mg dose group. Gastrointestinal disorders were also reported at a higher exposure adjusted incidence in the SEK 300 mg dose group (36.2 AEs per 100 PY; 28 AEs/77.4 PY) than in the SEK 150 mg group (26.5 AEs per 100 PY; 99 AEs/373.7 PY) and the SEK 75 mg dose arm (24.8 AEs per 100 PY; 88 AEs/354.4 PY).

When examining common AEs by PT, there were some potentially significant differences between the 3 SEK doses – refer to Table 29. In particular, 5 PTs within the SOC of infection showed a SEK dose proportional increase in incidence, the PTs of URTI, bronchitis, sinusitis, pharyngitis and oral herpes. In addition, 2 PTs within the SOC of skin and subcutaneous disorders (pruritus and rash) occurred at a higher incidence in the higher doses of SEK 150 mg and 300 mg dose groups versus the SEK 75 mg cohort.

Table 29: Exposure Adjusted Incidence of the most common Adverse Events by Preferred Term (≥2.0% in the combined SEK dataset) over Entire Treatment Period of Phase 3 PsA Studies.

Preferred Term	Any AIN457 75mg N=391 n/EX (IR)	Any AIN457 150mg N=438 n/EX (IR)	Any AIN457 300mg N=145 n/EX (IR)	Any AIN457 N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
- Any preferred term	296/158.7 (186.5)	342/147.0 (232.6)	94/42.3 (222.3)	732/348.0 (210.3)	181/56.6(319.6)
Upper respiratory tract infection	59/384.1 (15.4)	69/398.9 (17.3)	18/84.1 (21.4)	146/867.2 (16.8)	18/102.3 (17.6)
Nasopharyngitis	64/370.3 (17.3)	61/396.1 (15.4)	15/85.1 (17.6)	140/851.6 (16.4)	19/101.4 (18.7)
Headache	30/394.3 (7.6)	29/421.2 (6.9)	8/84.9 (9.4)	67/900.4 (7.4)	12/102.7 (11.7)
Back pain	28/400.7 (7.0)	18/431.1 (4.2)	3/89.2 (3.4)	49/921.0 (5.3)	5/104.1 (4.8)
Diarrhoea	18/406.5 (4.4)	21/426.6 (4.9)	6/88.1 (6.8)	45/921.3 (4.9)	9/103.4 (8.7)
Bronchitis	11/411.8 (2.7)	22/430.1 (5.1)	5/88.1 (5.7)	38/930.0 (4.1)	8/103.7 (7.7)
Hypertension	21/405.3 (5.2)	13/435.7 (3.0)	4/87.6 (4.6)	38/928.6 (4.1)	8/103.5 (7.7)
Arthralgia	17/407.8 (4.2)	16/435.4 (3.7)	4/88.4 (4.5)	37/931.6 (4.0)	7/104.5 (6.7)
Psoriatic arthropathy	18/410.4 (4.4)	17/435.7 (3.9)	2/89.6 (2.2)	37/935.7 (4.0)	3/104.7 (2.9)
Nausea	18/407.3 (4.4)	12/435.7 (2.8)	5/87.2 (5.7)	35/930.2 (3.8)	6/103.9 (5.8)
Sinusitis	11/413.1 (2.7)	15/437.1 (3.4)	9/87.2 (10.3)	35/937.4 (3.7)	6/104.6 (5.7)
Urinary tract infection	10/413.8 (2.4)	21/427.2 (4.9)	3/88.6 (3.4)	34/929.5 (3.7)	6/104.1 (5.8)
Cough	10/412.4 (2.4)	20/429.3 (4.7)	3/88.0 (3.4)	33/929.7 (3.5)	8/103.7 (7.7)
Psoriasis	18/409.5 (4.4)	11/440.2 (2.5)	2/88.7 (2.3)	31/938.4 (3.3)	5/104.2 (4.8)
Gastroenteritis	9/413.9 (2.2)	17/432.5 (3.9)	3/88.8 (3.4)	29/935.1 (3.1)	3/105.1 (2.9)
Pharyngitis	10/413.2 (2.4)	13/433.8 (3.0)	5/88.9 (5.6)	28/935.8 (3.0)	0/105.6 (0.0)
Hypercholesterolaemia	13/406.8 (3.2)	12/432.2 (2.8)	2/89.2 (2.2)	27/928.2 (2.9)	6/104.0 (5.8)
Oropharyngeal pain	11/411.8 (2.7)	10/437.1 (2.3)	4/88.2 (4.5)	25/937.1 (2.7)	8/104.1 (7.7)
Oral herpes	7/415.5 (1.7)	12/434.2 (2.8)	5/87.4 (5.7)	24/937.2 (2.6)	4/104.4 (3.8)
Vomiting	15/409.0 (3.7)	7/441.0 (1.6)	2/88.4 (2.3)	24/938.4 (2.6)	3/104.8 (2.9)
Fatigue	11/409.0 (2.7)	10/439.4 (2.3)	2/89.5 (2.2)	23/937.9 (2.5)	7/103.8 (6.7)
Dyspepsia	6/416.2 (1.4)	14/434.3 (3.2)	1/89.5 (1.1)	21/940.0 (2.2)	4/105.0 (3.8)
Pruritus	8/415.0 (1.9)	10/435.3 (2.3)	3/88.5 (3.4)	21/938.9 (2.2)	4/104.9 (3.8)
Rash	7/413.9 (1.7)	9/438.0 (2.1)	5/88.9 (5.6)	21/940.9 (2.2)	11/103.2 (10.7)
Alanine aminotransferase increased	5/414.5 (1.2)	12/436.8 (2.7)	3/88.1 (3.4)	20/939.4 (2.1)	4/105.0 (3.8)
Gastrooesophageal reflux disease	7/413.2 (1.7)	9/440.7 (2.0)	3/88.7 (3.4)	19/942.5 (2.0)	2/104.9 (1.9)

Regarding infection, the exposure adjusted incidence rates of infection per 100 PY was 95.1 in the SEK 300 mg treatment group, 89.1 in the SEK 150 mg arm and 72.9 in the SEK 75 mg group. URTI was the common type of infection in all 3 SEK treatment cohorts and occurred at a slightly higher incidence in the SEK 300 mg dose group (55.6 events per 100 PY) compared to the 2 other SEK treatment groups (44.3 events per 100 PY in the 150 mg arm and 42.2 events per 100 PY in the 75 mg dose group). A total of 15 cases of Candida infection were reported for SEK treated patients (versus 0 in the PBO cohort), with 5 cases occurring in the first 16 weeks and 10 more cases thereafter. Dose dependency was observed in the exposure-adjusted incidence of Candida infection – 1.2 per 100 PY (5 AEs/417 PY) in the SEK 75 mg group, 1.6 per 100 PY (7 AEs/440.3 PY) in the SEK 150 mg arm and 3.4 per 100 PY (3 AEs/88.5 PY) in the SEK 300 mg group. Twelve of the 15 cases were oral candidiasis. Apart from 1 SAE, all other Candida infections were rated of mild or moderate severity, resolved with standard treatment (typically, oral fluconazole) and did not result in treatment discontinuation. In addition to the 15 Candida

infections, 3 cases of opportunistic infection were identified by a broader search of the safety dataset over the entire treatment period. This included 1 case of disseminated cutaneous herpes zoster infection (SEK 75 mg SC therapy after IV loading) and 2 cases of oesophageal candidiasis (1 case each in the SEK 150 mg and 300 mg dose groups). All 3 opportunistic infections were rated as moderate in severity, resolved with standard treatment and did not lead to permanent discontinuation from SEK. Herpes viral infections occurred in a higher proportion of patients in the SEK 300 mg dose group (4.8%) than the other 2 SEK dose arms (3.1% in the SEK 75 mg group and 3.4% in the 150 mg arm) and PBO group (1.3%). The majority of herpes infections (~70% in each group) were orally located. None meet the criteria for SAE. Infections affecting the skin and subcutaneous tissues were relatively uncommon (7.6-11.9% incidence over 52 weeks in the SEK treatment groups versus 2.0% in the PBO arm). The most common types of skin infection were paronychia, otitis externa and cellulitis. No cases of reactivated latent TB were observed in the entire treatment period.

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

The overall incidence of AEs up to week 16 was higher for all SEK dose groups except SEK 75 mg SC therapy (57.5%; 42/73) compared to PBO (58.7%; 115/196). At 16 weeks, the frequency of AEs was 65.3% (47/72) in the SEK 150 mg SC group of Study F2310, 66.9% (83/124) in the SEK 10 mg/kg-75 mg arm and 69.6% (87/125) in the SEK 10 mg/kg-150 mg group. The 16-week rate of AEs in the pooled SEK dataset was 65.7% (259/394). For the majority of SOC types, the incidence of AEs up to week 16 was similar between the 4 SEK dose groups and PBO. The higher overall rate of AEs in the SEK treatment groups versus PBO is primarily explained by the higher frequency of infections (mainly, nasopharyngitis) and to a lesser extent AEs in the SOCs of metabolism and nutrition disorders (mainly, dyslipidaemia) and abnormal investigations – refer to Table 30. Lipid profile changes and abnormal investigations will be discussed below in this report.

Table 30: Short Term Adverse Events by SOC in the Phase 3 Ankylosing Spondylitis Studies.

Primary system organ class	AIN457 75mg N=73 n (%)	AIN457 150mg N=72 n (%)	AIN457 10mg/kg -75mg N=124 n (%)	AIN457 10mg/kg -150mg N=125 n (%)	Any AIN457 N=394 n (%)	Placebo N=196 n (%)
- Any primary system organ class	42 (57.5)	47 (65.3)	83 (66.9)	87 (69.6)	259 (65.7)	115 (58.7)
Infections and infestations	22 (30.1)	24 (33.3)	31 (25.0)	43 (34.4)	120 (30.5)	35 (17.9)
Gastrointestinal disorders	8 (11.0)	9 (12.5)	27 (21.8)	23 (18.4)	67 (17.0)	32 (16.3)
Metabolism and nutrition disorders	3 (4.1)	5 (6.9)	22 (17.7)	15 (12.0)	45 (11.4)	18 (9.2)
Nervous system disorders	6 (8.2)	8 (11.1)	9 (7.3)	19 (15.2)	42 (10.7)	22 (11.2)
Musculoskeletal and connective tissue disorders	4 (5.5)	7 (9.7)	12 (9.7)	6 (4.8)	29 (7.4)	27 (13.8)
Respiratory, thoracic and mediastinal disorders	3 (4.1)	6 (8.3)	8 (6.5)	12 (9.6)	29 (7.4)	18 (9.2)
General disorders and administration site conditions	4 (5.5)	9 (12.5)	9 (7.3)	6 (4.8)	28 (7.1)	15 (7.7)
Skin and subcutaneous tissue disorders	4 (5.5)	6 (8.3)	5 (4.0)	13 (10.4)	28 (7.1)	13 (6.6)
Investigations	1 (1.4)	8 (11.1)	9 (7.3)	6 (4.8)	24 (6.1)	10 (5.1)
Blood and lymphatic system disorders	0	0	13 (10.5)	9 (7.2)	22 (5.6)	6 (3.1)
Injury, poisoning and procedural complications	2 (2.7)	3 (4.2)	7 (5.6)	5 (4.0)	17 (4.3)	13 (6.6)
Eye disorders	1 (1.4)	0	6 (4.8)	7 (5.6)	14 (3.6)	6 (3.1)
Vascular disorders	2 (2.7)	2 (2.8)	2 (1.6)	6 (4.8)	12 (3.0)	3 (1.5)
Cardiac disorders	2 (2.7)	0	3 (2.4)	6 (4.8)	11 (2.8)	4 (2.0)
Psychiatric disorders	2 (2.7)	3 (4.2)	5 (4.0)	0	10 (2.5)	7 (3.6)
Renal and urinary disorders	1 (1.4)	0	3 (2.4)	4 (3.2)	8 (2.0)	4 (2.0)
Hepatobiliary disorders	0	0	3 (2.4)	2 (1.6)	5 (1.3)	3 (1.5)
Ear and labyrinth disorders	0	0	1 (0.8)	2 (1.6)	3 (0.8)	6 (3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.4)	0	2 (1.6)	3 (0.8)	1 (0.5)
Congenital, familial and genetic disorders	1 (1.4)	0	0	0	1 (0.3)	0
Endocrine disorders	0	0	1 (0.8)	0	1 (0.3)	1 (0.5)
Reproductive system and breast disorders	0	0	0	1 (0.8)	1 (0.3)	4 (2.0)
Immune system disorders	0	0	0	0	0	1 (0.5)

Infection was the common type of AE by SOC and this occurred at a higher frequency in the pooled SEK cohort (30.5%; 120/394) compared to PBO treated subjects (17.9%; 35/196) in the first 16 weeks of study follow-up. The incidence of infections was similar across the 4 SEK dose groups: 30.1% (22/73) in the SEK 75 mg SC group of Study F2310, 33.3% (24/72) in the SEK 150 mg SC arm of Study F2310, 25.0% (31/124) in the SEK 10 mg/kg-75 mg group of Study F2305 and 34.4% (43/125) in the SEK 10 mg/kg-150 mg dose arm of Study F2305. The most common types of infection by PT were URTI (18.0% [71/394] in the pooled SEK cohort versus 10.7% [21/296] in the PBO group) and nasopharyngitis (11.2% [44/394] in the pooled SEK population versus 6.1% [12/296] in the PBO arm). No clear SEK dose relationship for the incidence of URTI was seen across the SC dose regimens (15.1% for SEK 75 mg versus 16.7% for SEK 150 mg) or the IV dose regimens (19.4% in the SEK 75 mg group versus 19.2% in the SEK 150 mg arm). Two patients treated with SEK 75 mg injections developed Candida infections (one was oral in location, and the other was genital) in the first 8 weeks of therapy. Both cases were rated mild in severity and did not lead to treatment discontinuation. Herpes viral infections were more common in the pooled SEK treatment cohort (2.0%) versus PBO (0) with the majority of these infections being oral in location. No herpes infections resulted in treatment discontinuation. No opportunistic infections such as reactivation of latent TB or systemic fungal infection were experienced in the short term of either Phase 3 Study.

The 6 most frequent individual types of AEs by PT (incidence ≥2.0% in the pooled SEK population) in the Phase 3 AS studies up to week 16 were: nasopharyngitis (11.2% [44/394] in the pooled SEK cohort versus 6.1% [12/196] in the PBO group), dyslipidaemia (6.6% [26/394] in the pooled SEK group versus 3.6% [7/196] in the PBO arm), headache (6.6% [26/394] in the pooled SEK cohort versus 6.6% [13/196] in the PBO group), nausea (3.8% [15/394] in the pooled SEK group versus 2.6% [5/196] in the PBO arm), oropharyngeal pain (3.8% [15/394] in the pooled SEK cohort versus 4.1% [8/196] in the PBO group) and diarrhoea (3.0% [12/394] in the pooled SEK group versus 3.6% [7/196] in the PBO arm). Three of the 6 most common AEs by PT were more common in the SEK treatment population versus PBO, but their frequency was not dose dependent with SEK. Three other common types of AEs by PT were more common in the SEK treatment population compared to PBO, but neither displayed a dose dependent relationship with SEK. The 3 AE types were hypertension (2.0% [8/394] for pooled SEK therapy versus 0 in the PBO arm), oral herpes infection (1.3% [5/394] for the pooled SEK group versus 0 in the PBO cohort) and injection site pain (1.0% [4/394] for pooled SEK therapy, all in the SEK 150 mg SC group of Study F2310, versus 0.5% [1/196] in the PBO arm). Six of the 8 cases of hypertension identified in the SEK treated subjects had a prior history of elevated blood pressure.

The overall AE profile between weeks 0 and 8 versus between weeks 8 and 16 (to examine for a potential effect of the SEK loading regimen) did not demonstrate any significant differences in the incidence and type of AEs by treatment period.

Entire treatment period of phase 3 studies

Over the entire treatment period, the incidence of AEs was comparable between the SEK 150 mg group (84.0%; 241/287) and the SEK 75 mg dose arm (79.2%; 225/284). Similar to the week 16 data, the 2 most common types of AEs by SOC over the entire treatment period were infections (51.2% [147/287] in the SEK 150 mg group and 52.5% [149/284] in the SEK 75 mg dose arm) followed by gastrointestinal disorders (26.1% [75/287] in the SEK 150 mg group and 28.2% [80/284] in the SEK 75 mg dose arm). There were no significant differences between the 2 SEK doses for the common types of AEs by SOC; however, there were 2 dose related differences when examining common AEs by PT. Three PTs within the SOC of skin and subcutaneous disorders were higher in the SEK 150 mg dose group versus the SEK 75 mg cohort: pruritus (2.4% versus 1.4%, respectively), dermatitis (1.7% versus 0.7%, respectively) and dermatosis (1.0% versus 0, respectively). Within the SOC of abnormal investigations, the PTs of hypercholesteraemia (2.8% versus 1.4%) and hyperlipidaemia (2.1% versus 1.1%) occurred at a higher frequency in the SEK 150 mg dose group. Other noteworthy AEs by PT that were reported in the entire treatment period, at an equal incidence in both SEK dose cohorts, were nasopharyngitis (18.7%; 107/571), diarrhoea (9.3%; 53/571), URTI (9.1%; 52/571), influenza (5.8%; 33/571), leucopenia (3.9%; 22/571), oral herpes (2.6%; 15/571), urinary tract infection (2.5%; 14/571), neutropenia (2.1%; 12/571) and increased serum transaminases (1.8%; 10/571).

Regarding infection, the exposure adjusted incidence rates in the 2 SEK treatment groups (67.9-68.1 infections per 100 PY) were slightly higher than that observed in the PBO arm (63.8 infections per 100 PY). URTI was the common type of infection in all 3 treatment cohorts at a slightly higher incidence in the 2 SEK dose groups (38.7-39.1 events per 100 PY) compared to PBO (35.3 events per 100 PY). A total of 6 cases of Candida infection were reported for SEK treated patients (versus 0 in the PBO cohort), with 2 cases occurring in the first 8 weeks and the other 4 thereafter (2 in each SEK dose group). Three of the 6 cases were oral candidiasis. All Candida infections were rated of mild severity, resolved with standard treatment and did not result in withdrawal. One opportunistic infection (disseminated cutaneous herpes zoster infection) was identified in the entire treatment period. This affected a person who received SEK 75 mg SC injections after IV loading in Study F2305. The infection was rated moderate in severity, resolved with acyclovir and did not lead to treatment discontinuation. Other infections affecting the skin and subcutaneous tissues were uncommon (9.2-10.8% incidence over 52

weeks in the SEK treatment groups versus 1.5% in the PBO arm). The most common types of skin infection were folliculitis and tinea pedis (occurring in 4 patients each). No cases of reactivated latent TB were observed in the entire treatment period.

8.4.1.2. Other studies

All SEK treatment data pool

The general profile (incidence and type) of AEs recorded in the induction phases (typically first 6-12 weeks) was similar between the all SEK treatment data pool and that observed in the pivotal PBO-controlled trials in PsA and AS. There was no new type or increased rate of AEs (overall or by SOC) in the expanded safety data pool. The incidence of total AEs was highest with the SEK 300 mg and 150 mg injections versus PBO in the PSOR trials. This imbalance was driven primarily by an increased rate of infections with SEK, as per the pivotal Phase 3 studies in PsA and AS. Moreover, there were no new patterns or treatment differences observed in the larger SEK treatment dataset compared to the data in the Phase 3 PsA and AS studies.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

Psoriatic arthritis

Short term period (16 weeks) of phase 3 studies

In the first 16 weeks of the Phase 3 PsA studies, the overall incidence of treatment related AEs (as rated by the site investigators) was higher for the SEK 300 mg SC group (25.0%; 25/100) compared to the 2 other SEK SC dose arms (21.2% [21/99] in the 75 mg SC dose group and 18.0% [18/100] in the 150 mg SC arm) and the PBO group (20.7%; 62/300). At 16 weeks, the frequency of treatment related AEs was also higher in the higher dose SEK group with IV loading at 26.7% (54/202) in the SEK 10 mg/kg-150 mg arm compared to 22.3% (45/202) in the SEK 10 mg/kg-75 mg group. Up to week 16, the profile of AEs considered to be related to study treatment was similar to that observed for all treatment emergent AEs. The difference in the overall incidence of treatment related AEs between each of the SEK dose groups and also when compared to PBO was primarily explained by a higher rate of infections in the SEK 300 mg SC group (13.0%; 13/100) and SEK 10 mg/kg-150 mg arm (14.4%; 29/202) compared to an infectious frequency of 9.4-12.0% in all of the other SEK treatment groups and 9.0% (27/300) in the PBO arm. Regarding individual types of infection, there were small differences between the treatment groups for the incidence of respiratory tract (e.g. 2.0% in the SEK 300 mg SC group versus zero in the SEK 75 mg and 150 mg SC groups as well as PBO) and oral herpes infection (e.g. 2.0% in the SEK 300 mg SC group versus 0-1% in the SEK 75 mg and 150 mg SC groups as well as PBO), which explained the result. There was a small increased frequency of treatment related AEs in the SOC of skin and subcutaneous disorders for the SEK 300 mg SC group (5.0%; 5/100) and SEK 10 mg/kg-150 mg arm (4.0%; 8/202) compared to a frequency of 1.0-3.0% in all of the other SEK treatment groups and 3.3% (10/300) in the PBO arm. Regarding individual types of events (such as pruritus, dermatitis and urticaria) to explain this treatment related difference, no clear pattern of AEs by PT could be identified.

Entire treatment period of phase 3 studies

Over the entire treatment period, there was a higher overall incidence of treatment related AEs in the SEK dose groups (29.0% [42/145] in the 300 mg dose arm, 31.7% [139/438] in the 150 mg group and 28.9% [113/391] in the SEK 75 mg arm) compared to the PBO group (21.3%; 64/300). Similar to the week 16 treatment related AE data, the frequency difference between SEK and PBO therapy was mainly explained by a higher incidence of infectious AEs in the SEK dose groups (16.6% [24/145] in the 300 mg dose arm, 20.8% [91/438] in the 150 mg group and 17.9% [70/391] in the SEK 75 mg arm) compared to the PBO group (9.7%; 29/300). Upper respiratory tract infection and nasopharyngitis were the 2 most common types of infection, followed by lower respiratory tract infections, urinary tract infections, sinusitis, oral herpes,

bronchitis and pharyngitis (all occurring at relatively low rates, i.e. ≤1.0% incidence) contributed to this imbalance. No clear dose response relationship for SEK was seen for the overall rate of treatment related AEs, as well as the individual types of AEs by SOC and/or PT nomenclature.

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

Up to week 16, the profile of AEs considered to be related to study treatment was similar to that observed for all treatment emergent AEs. The incidence of AEs related to study treatment was comparable between the pooled SEK cohort (25.9%; 102/394) and the PBO group (26.5%; 52/196). However, patients in the SEK 150 mg SC group (26.4%; 19/72) reported AEs related to study treatment more frequently than the SEK 75 mg SC arm (17.8%; 13/73). This difference was explained by the following types of AEs: injection site pain (5.6% versus 0, respectively), nasopharyngitis (4.2% versus 1.4%), headache (4.2% versus 1.4%), oral herpes infection (2.8% versus 0) and pain in extremity (2.8% versus 0). Furthermore, the frequency of overall AEs related to study treatment was higher in the IV SEK loading groups (22.6% [28/124] in the SEK 10 mg/kg-75 mg group and 33.6% [42/125] in the SEK 10 mg/kg-150 mg dose arm) compared with the SC loading regimens (17.8-26.4% incidence). The main differences between the IV and SC loading groups were the different incidences of AEs by PT: leucopenia (5.6% versus 0), headache (4.8% versus 2.8%), dyslipidaemia (1.6% versus 0) and fatigue (1.6% versus 0). There was no discernible difference between the IV and SC loading regimens for the overall incidence and type of infections.

Entire treatment period of phase 3 studies

Over the entire treatment period, a higher rate of AEs related to study treatment was observed in the SEK 150 mg dose group (44.9%; 129/287) compared to the SEK 75 mg arm (34.9%; 99/284) and PBO group (27.6%; 54/196). The AEs that showed an increased incidence of ≥2% in the SEK 150 mg group compared with the SEK 75 mg dose arm were nausea (2.4% versus 0.4%, respectively), nasopharyngitis (7.3% versus 3.5%), pharyngitis (3.8% versus 0.7%), headache (5.2% versus 1.8%) and oral herpes infection (2.8% versus 0.7%).

8.4.2.2. Other studies

All SEK treatment data pool

Treatment-related AEs in the all SEK treatment pool showed a similar pattern to that reported in the Phase 3 PsA and AS studies. No new safety information was observed from the expanded dataset.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

Psoriatic arthritis

Short term period (16 weeks) of phase 3 studies

Up to week 16, no death was recorded in the Phase 3 PsA trials. In addition, the incidence of SAEs was low and similar among the 6 treatment groups with no clear dose dependent increase in SAEs for SEK. The incidence of SAEs was 4.0% (4/99) in the SEK 75 mg SC group, 1.0% (1/100) in the SEK 150 mg SC arm, 5.0% (5/100) in the SEK 300 mg SC group, 2.5% (5/202) in the SEK 10 mg/kg-75 mg group, 4.5% (9/202) in the SEK 10 mg/kg-150 mg arm and 4.0% (12/300) in the PBO group (versus 3.4% [24/703] for the pooled SEK cohort). The incidence of SAEs was not higher in the groups who received SEK loading regimens (IV or SC) compared with those who didn't receive loading therapy (i.e. the PBO switch patients). Furthermore, the incidence and type of SAEs was similar between weeks 0 and 8 versus weeks 8-16. Most of the SAEs were single event types, however, there were some SAE types that affected multiple individuals with potential treatment related differences. The most common type of SAE by SOC

was infection, which affected a total of 9 SEK treated subjects (1.3% of 703; 5 of whom received IV loading and 3 received SEK 300 mg SC injections) compared to 1 PBO treated subject (0.3% of 300). Five of the 9 infection related SAEs in SEK treated subjects were skin or soft tissue infections (e.g. erysipelas) and 3 were lung infections (e.g. pneumonia or lung abscess). The other infection was osteomyelitis in a subject who received SEK 300 mg SC injections. A total of 5 patients (3 received SEK IV loading and 2 were treated with PBO) developed gastrointestinal SAEs. These included 1 case of Crohn's disease in a PBO-treated patient. There were no cases of inflammatory bowel disease in SEK treated individuals. Four patients developed cardiac SAEs (3 treated with SEK and 1 in the PBO arm), 2 of which were related to coronary artery disease (1 received SEK and the other was in the PBO group). One patient treated with SEK 75 mg SC injections in Study F2312 developed squamous cell carcinoma of the skin.

Entire treatment period of phase 3 studies

One patient died in the extended follow-up period of the 2 pivotal Phase 3 PsA trials. The death involved a [information redacted] subject who received SEK 75 mg SC injections (after IV loading) in Study F2306. She died of intracranial haemorrhage on study day 248 and had multiple risk factors for the event including a history of hypertension, diabetes mellitus, chronic renal impairment, atrial fibrillation, congestive heart failure and a previous thromboembolic stroke. The death was judged as being not related to study medication, which is an appropriate assessment.

Over the entire treatment period, the exposure-adjusted incidence rates of SAEs (overall and by SOC type) were low and comparable between the 3 SEK treatment groups and the PBO arm. The overall frequency of SAEs was 8.4 per 100 PY (34 SAEs/406.7 PY) in the SEK 75 mg group, 9.8 per 100 PY (41 SAEs/420.3 PY) in the SEK 150 mg arm, 8.1 per 100 PY (7 SAEs/86.6 PY) in the SEK 300 mg group and 13.6 per 100 PY (14 SAEs/102.8 PY) in the PBO arm. Infections remained the most SOC type of SAE in all treatment groups occurring at an exposure adjusted incidence rate of 2.2-2.9 per 100 PY in all groups except the high dose SEK arm (4.5 per 100 PY in the SEK 300 mg dose group). The pattern of infection related SAEs did not alter over time compared to those observed in the first 16 weeks of treatment follow-up. There were 2 cases of Crohn's disease recorded over the entire treatment period of the Phase 3 PsA studies. In addition to the 1 case identified in the first 16 weeks, there was 1 additional case in a patient treated with SEK 75 mg SC injections in Study F2312.

In addition to the 1 malignancy identified in the first 16 weeks of the 2 Phase 3 studies, another patient treated with SEK 75 mg injections after IV loading developed basal cell skin cancer, which was rated as a non-serious AE. In addition, one subject in the PBO group was diagnosed as having an intraductal proliferative breast lesion. The exposure adjusted incidence rate of malignancy was low and identical between the pooled SEK treatment cohort and PBO at 0.3 events per 100 PY.

An independent adjudication committee was established to evaluate all major adverse cardiovascular events (MACE). A total of 8 MACE cases (7 in the SEK 75 mg group, 1 in the SEK 150 mg arm and none in the PBO group) were recorded over the entire treatment period of the Phase 3 PsA studies. Three of the 8 cases were myocardial infarction (2 in the SEK 75 mg group and 1 in the SEK 150 mg arm) and the other 5 MACE events were various types of cerebrovascular accident. All of the patients who experienced MACE had 2 or more significant risk factors for cardiovascular events (such as hypertension and hyperlipidaemia) and the PsA population as a whole has an increased risk of MACE. The exposure adjusted incidence rate of MACE for SEK treatment (pooled dataset) was low at 0.7 events per 100 PY.

No SAEs of angioedema, anaphylaxis or severe hypersensitivity reactions were reported during the entire treatment period of the Phase 3 PsA studies.

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

Up to week 16, 2 deaths were recorded in the Phase 3 AS study program and both were considered to be unrelated to study treatment. A [information redacted] subject who received SEK 75 mg SC injections in Study F2310 died on study day 29 of acute myocardial infarction (autopsy confirmed). This subject had multiple risk factors for coronary ischaemia including long-term smoking (ongoing) and dyslipidaemia. The patient had previously received infliximab for 6 years (ceased 2 months prior to study commencement) and multiple NSAID drugs in past (unknown duration). The other death involved a [information redacted] subject who received PBO therapy in Study F2305. They committed suicide on study day 80. There was no prior history of mental illness and the patient was admitted to hospital with severe depression on study day 67. He was treated with anti-depressants, lorazepam and psychotherapy and was discharged on study day 79. This subject had received etanercept for 5 years prior to study involvement (ceased 1 month prior to baseline).

In the first 16 weeks of the 2 Phase 3 AS studies, the incidence of SAEs was low and similar among the 5 treatment groups with no dose dependent increase in SAEs for SEK. The incidence of SAEs was 5.5% (4/73) in the SEK 75 mg SC group, 5.6% (4/72) in the SEK 150 mg SC arm, 1.6% (2/124) in the SEK 10 mg/kg-75 mg group, 2.4% (3/125) in the SEK 10 mg/kg-150 mg arm and 4.1% (8/196) in the PBO group (versus 3.3% [13/394] for the pooled SEK cohort). Interestingly, the IV loading regimens for SEK had a lower incidence of SAEs, even when the sponsor did an additional analysis examining whether the incidence and type of SAEs were different between weeks 0 and 8 versus weeks 8-16. Most of the SAEs were single event types, however, there were some SAE types that affected multiple individuals with potential treatment related differences. Three patients, all treated with SEK 75 mg SC injections in Study F2310, developed gastrointestinal SAEs. These included 1 case each of Crohn's disease, ulcerative colitis and microscopic colitis. In addition, 1 patient treated with SEK 150 mg injections in Study F2305 (after IV loading) developed uveitis. There were also 2 noteworthy SAEs in the SEK 150 mg group of Study F2310 – malignant melanoma and raised hepatic enzymes (≥5-fold increase in serum transaminases on study day 57, which persisted for >2 weeks and resulted in treatment discontinuation). In the PBO treatment group, 2 patients developed depression (1 committed suicide), which raises the possibility that inactive treatment and/or treatment withdrawal (e.g. pain and function impairment) may have been co-factor in the pathogenesis of depression. Another subject in the PBO group developed B-cell lymphoma in the first 16 weeks.

Entire treatment period of phase 3 studies

A total of 3 patients died (2 already discussed above) in the 2 pivotal Phase 3 AS trials. The third death involved a 39-year-old male who received SEK 75 mg SC injections (after IV loading) in Study F2305. His death was attributed to respiratory failure secondary to pulmonary fibrosis and cardiac failure on study day 706 (i.e. ~2 years on active SEK treatment). His risk factors included long-term smoking and a history of arterial hypertension.

Over the entire treatment period of the 2 Phase 3 AS studies, the incidence of SAEs remained low and similar between the 2 SEK treatment groups. The overall incidence of SAEs was 9.5% (27/284) in the SEK 75 mg group and 8.7% (25/287) in the SEK 150 mg arm. The exposure-adjusted incidence rate of SAEs was 8.2 per 100 PY (27 SAEs/327.3 PY) for SEK 75 mg therapy and 7.5 per 100 PY (25 SAEs/332.0 PY) for SEK 150 mg versus 12.8 per 100 PY (8 SAEs/62.7 PY) in the PBO group. The incidence of serious infection was low for both doses of SEK (3 infection related SAEs in each group) with an exposure-adjusted incidence of 0.9 per 100 PY (versus 0 in the PBO cohort). The most common location for serious infection was the respiratory tract (upper or lower).

Over the entire treatment period, the exposure-adjusted incidence rate of serious gastrointestinal disorders was higher in both SEK treatment groups compared to PBO: 1.8 per

100 PY (6 SAEs/341 PY) in the SEK 75 mg group and 1.2 per 100 PY (4 SAEs/344 PY) in the SEK 150 mg arm versus 0 in the PBO group. There were 8 cases of inflammatory bowel disease (IBD) over the entire treatment period of the Phase 3 AS studies. In addition to the 3 cases identified in the first 16 weeks, there were 2 additional cases of ulcerative colitis (both from the SEK 150 mg SC group of Study F2310) and 3 additional cases of Crohn's disease (2 from the SEK 10 mg/kg-75mg group of Study F2305 and 1 from the SEK 150 mg SC arm of Study F2310). Four of the 8 IBD cases had a history of gastrointestinal disease or symptoms, suggesting that half of the reported cases were de-novo in occurrence.

In addition to the 2 malignancies identified in the first 16 weeks of the 2 Phase 3 studies, 3 other SEK treated patients (all involved in Study F2305) developed cancer (including skin tumours). They were individual cases of B-cell lymphoma (SEK 75 mg injections), breast cancer (SEK 150 mg therapy) and bladder carcinoma (SEK 150 mg injections). One patient in the PBO arm developed melanoma in the extended follow-up period. The exposure adjusted incidence rate of malignancy was low and similar between the 2 SEK treatment groups (0.3-0.9 events per 100 PY), as well as in comparison to the PBO arm (1.6 events per 100 PY).

An independent adjudication committee was established to evaluate all major adverse cardiovascular events (MACE). A total of 4 MACE cases (none in the PBO arm) were recorded over the entire treatment period of the Phase 3 AS studies. Three of the 4 cases were myocardial infarction (1 case each in the SEK 75 mg SC group, SEK IV-75 mg arm and SEK IV-150 mg therapy) and the other MACE was a cerebrovascular accident (PBO subject re-randomized to SEK 150 mg SC therapy in Study F2310). All of the patients who experienced MACE had 2 or more significant risk factors for cardiovascular events (smoking and hypertension) and the AS population as a whole has an increased risk of MACE. One of the 3 myocardial infarctions occurred in the first 8 weeks of treatment, but all of the other MACE cases occurred >8 months after treatment commencement. The exposure adjusted incidence rate of MACE was low and similar between the 2 SEK treatment groups (0.3-0.7 events per 100 PY).

No SAEs of angioedema, anaphylaxis or severe hypersensitivity reactions were reported during the entire treatment period of the Phase 3 AS studies.

8.4.3.2. Other studies

All SEK treatment data pool

This large data pool, which includes all patients treated with SEK in 42 studies across various autoimmune conditions, maximises the probability of observing rare but serious AEs such as MACE, malignancy, all cause mortality and inflammatory bowel disease.

In the pivotal Phase 3 PSOR trials, 3 deaths have been reported. One patient with concomitant PsA died of unknown cause during the extended treatment follow-up period. This subject had initially received PBO and then switched to SEK 300 mg injections at week 12 because of insufficient response. The other 2 deaths in PSOR patients were as a result of cardiopulmonary arrest (SEK 150 mg therapy) and alcohol poisoning (switched from PBO to SEK 300 mg therapy).

There was no imbalance between the exposure adjusted incidence of malignancy between SEK (0.95 per 100 PY; 59 reports/6242 PY) and PBO treated subjects (1.55 per 100 PY; 8 reports/515 PY) over the entire treatment period in all SEK studies across multiple indications. In addition, when specifically examining the exposure adjusted incidence of skin malignancies, this tumour type showed a comparable exposure adjusted incidence of occurrence (0.59 per 100 PY for all SEK groups [including 25 cases of basal cell carcinoma, 7 reports of squamous cell carcinoma and 5 cases of malignant melanoma] versus 0.97 per 100 PY for PBO [including 2 cases of basal cell carcinoma, 1 report of squamous cell carcinoma and no cases of malignant melanoma]). The other malignancies reported in the all SEK treatment dataset affected 1-3 cases at incidences consistent with the matched population. In descending order of frequency they include breast cancer (n=3), bladder cancer (n=3), thyroid cancer (n=2), colon cancer

(n=2), B-cell lymphoma (n=2) and various other individual case reports (e.g. lung, renal and ovarian cancer).

A total of 30 MACE reports have been recorded in the all SEK treatment database at an exposure adjusted incidence rate of 0.40 per 100 PY, which is comparable to that observed in the PBO population (0.39 MACE per 100 PY; 2 reports in 1665 patients with a total exposure of 515 PY). A total of 5 deaths due to cardiovascular disease and 1 additional mortality due to haemorrhagic stroke have been reported in the all SEK treatment safety set. Myocardial infarction has affected 15 SEK treated subjects at an incidence of 0.24 per 100 PY versus 1 PBO treated patient (incidence of 0.19 per 100 PY). No dose response relationship for the incidence of MACE has been identified with SEK.

In the all SEK treatment dataset, there have been 35 reports of inflammatory bowel disease in a total population cohort of 6200 subjects, including 18 cases of confirmed Crohn's disease and 9 reports of ulcerative colitis. However, the exposure adjusted incidence rate of inflammatory bowel disease in the SEK treated cohort is lower (0.56 AEs per 100 PY) than the observed rate in the PBO population (1.16 AEs per 100 PY; 6 cases in 1665 patients, including 4 cases of Crohn's disease and 1 report of ulcerative colitis).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

Psoriatic arthritis

Short term period (16 weeks) of phase 3 studies

In the Phase 3 PsA studies, the rate of discontinuation due to AEs at 16 weeks was low and comparable across the 6 treatment groups. At 16 weeks, the frequency of premature withdrawal due to AEs was 2.0% (2/99) in the SEK 75 mg SC group of Study F2312, 0 in the SEK 150 mg SC group of Study F2312, 2.0% (2/100) in the SEK 300 mg SC group of Study F2312, 2.0% (4/202) in the SEK 10 mg/kg-75 mg arm of Study F2306, 1.5% (3/202) in the SEK 10 mg/kg-150 mg group of Study F2306 and 2.7% (8/300) in the PBO cohort. The 16-week rate of discontinuation due to AEs in the pooled SEK dataset was 1.6% (11/703). All AEs leading to discontinuation were single types of events. There were a few noteworthy AEs resulting in permanent discontinuation. One patient treated with SEK 75 mg SC injections in Study F2312 discontinued on study day 1 due to severe hyperlipidaemia, which was not suspected to be related to study medication. One subject treated with SEK 10 mg/kg loading following by 150 mg injections in Study F2306 ceased due to a severe, non-specified viral infection. Another subject treated with IV SEK 10 mg/kg and then 75 mg SC injections in Study F2306 prematurely discontinued due to angioedema. One patient each in the PBO group discontinued due to Crohn's disease, depression and exacerbation of PSOR.

AEs leading to dose interruption were slightly higher in the SEK SC treatment groups (8.0% for 300 mg, 8.0% for 150 mg and 5.1% for 75 mg) compared to PBO (6.0%; 5/196) and the IV SEK loading regimens (4.0-5.9%). The most common SOC type of AE leading to dose interruption was infection, which occurred at a slightly higher frequency in the SEK SC dose groups (5.0% for 300 mg therapy, 8.0% for 150 mg injections and 4.0% for 75 mg therapy) compared to 2.7% in the PBO cohort and 2.5-3.0% in the 2 IV SEK loading regimens. The most common types of infection (n=3-5 each) in SEK treated individuals resulting in dose interruptions were URTI, nasopharyngitis, sinusitis and urinary tract infection. There was also 1 case of herpes zoster in a subject treated with SEK 300 mg SC injections and 2 cases of leucopenia in subjects treated with IV SEK 10 mg/kg then 75 mg SC injections in Study F2306.

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 Phase 3 AS studies, the incidence of premature discontinuation due to AEs was 4.1% (16/391) in the SEK 75 mg cohort, 2.5% (11/438) in the SEK 150 mg dose group and 1.4% (2/145) in the SEK 300 mg cohort versus 3.3% (10/300) on

the PBO group. The were only 2 types of AEs leading to discontinuation which affected 2 or more subjects: Crohn's disease (1 case in the SEK 75 mg group and 1 in the PBO arm) and exacerbation of PsA (both treated with SEK – 1 with 75 mg injections and the other 150 mg therapy). There was also 1 case of colitis in a patient treated with SEK 75 mg therapy. One patient (36 year old Asian male) in the SEK 150 mg dose group of Study F2306 (after being re-randomised at week 16 for being a PBO non-responder) discontinued at day 141 (i.e. just after week 20 visit) due to drug induced liver injury. This patient was identified as having latent TB in the screening phase and received isoniazid just prior to randomisation. He had also been taking MTX continuously for >5 years. Baseline serum transaminases increased to 2-5 x ULN, prompting discontinuation from SEK. The hepatic enzyme abnormality slowly but incompletely resolved by study day 226. Isoniazid was also ceased. The AE causality assessment was confounded by the history of MTX and isoniazid use. Apart from the expected withdrawals due to malignancy and MACE, other single events of interest in the SEK treated subjects included angioedema (initial 16 weeks), hypersensitivity reaction and pneumonia.

The incidence of AEs leading to dose interruption over the entire treatment period was 9.5% (37/391) in the SEK 75 mg group, 11.4% (50/438) in the SEK 150 mg arm and 11.0% (16/145) in the SEK 300 mg cohort versus 6.3% (19/300) in the PBO group. Similar to what was observed in the first 16 weeks, the most common AE type resulting in dose delay was infections (6.9% in the SEK 75 mg group, 7.3% in the SEK 150 mg arm and 7.6% in the SEK 300 mg group). The pattern of infections was also similar in the extended treatment follow-up phase, being mainly URTI, nasopharyngitis and urinary tract infection.

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

The rate of discontinuation due to AEs at 16 weeks was higher in the PBO group (5.1%; 10/196) than any of the SEK treatment groups apart from SEK 150 mg SC therapy in Study F2310 (6.9%; 5/72). At 16 weeks, the frequency of premature withdrawal due to AEs was 4.1% (3/73) in the SEK 75 mg SC group of Study F2310, 1.6% (2/124) in the SEK 10 mg/kg-75 mg arm and 0.8% (1/125) in the SEK 10 mg/kg-150 mg group. The 16-week rate of discontinuation due to AEs in the pooled SEK dataset was 2.8% (11/394). All AEs leading to discontinuation were single events apart from 2 cases of withdrawal due to raised serum transaminases affecting 1 patient treated with SEK 150 mg SC injections in Study F2310 and the other subjects received SEK 10 mg/kg loading following by 75 mg injections in Study F2305. Another subject treated with SEK 10 mg/kg and then 75 mg SC injections in Study F2305 prematurely discontinued due to a reduced haemoglobin level. One subject in each SEK dose arm of Study F2310 withdrew due to IBD (1 case each of Crohn's disease and ulcerative colitis).

AEs leading to dose interruption were infrequent but higher in the pooled SEK cohort (6.6%; 26/394) compared to PBO (2.6%; 5/196). The most common SOC type of AE leading to dose interruption was infection, which occurred at a similar frequency in the 2 SEK SC dose groups (6.8% for 75 mg therapy and 5.6% for 150 mg injections). The most common types of infection (in declining order of frequency) resulting in dose interruptions were nasopharyngitis, pharyngitis, URTI and urinary tract infection.

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 Phase 3 AS studies, the incidence of premature discontinuation due to AEs was 3.9% (11/284) in the SEK 75 mg cohort and 7.0% (20/287) in the SEK 150 mg dose group. The type of AEs leading to discontinuation in more than 1 case included Crohn's disease (2 cases in the SEK 75 mg group), raised hepatic enzymes or serum transaminases (4 cases in total, 3 of which in the SEK 150 mg arm), pregnancy (2 cases in the SEK 150 mg group), reduced haemoglobin level (1 case in each SEK dose group) and non-specific dyspnoea (1 patient in each SEK arm). Apart from the expected withdrawals due to malignancy and MACE, other single events of interest (all in the SEK 150 mg dose cohort)

included colitis, herpes zoster infection, small intestinal obstruction, polyneuropathy and pulmonary cavitation.

The incidence of AEs leading to dose interruption over the entire treatment period was 12.3% (35/284) in the SEK 75 mg group and 14.3% (41/287) in the SEK 150 mg cohort. Similar to what was observed in the first 16 weeks, the most common AE type resulting in dose delay was infections (7.7% in the SEK 75 mg group and 9.8% in the SEK 150 mg arm). The pattern of infections was also similar in the extended treatment follow-up phase, being mainly URTI, nasopharyngitis and urinary tract infection.

8.4.4.2. Other studies

All SEK treatment data pool

In the induction phases (first 12-16 weeks) of the other SEK treatment studies, the rate of AEs causing discontinuation was comparable between the SEK, PBO and other active treatment groups (e.g. etanercept was used in 1 of the PSOR studies) with no dose effect observed for SEK in the overall rate of discontinuation due to AEs. The absolute incidence of AEs causing discontinuation over the entire treatment period in all SEK treatment data pool was low comparable between any SEK dose and active comparators (<4% incidence), but usually higher than PBO. The comparison of absolute incidence rates versus PBO over the entire treatment period is limited by the small number of patients receiving PBO treatment after week 12 in many studies and therefore the results should be interpreted with caution.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

Psoriatic arthritis

Short term period (16 weeks) of phase 3 studies

During the first 16 weeks, mild (grade 1) elevations in serum transaminases were seen slightly more frequently with SEK treatment (any dose regimen) compared to PBO. By 16 weeks, the incidence of raised ALT values was 15.8% (43/272) in the PBO group versus 18.6% (117/629) in the combined SEK treatment population (23.3% [21/90] in the SEK 75 mg SC group, 21.3% [19/89] in the SEK 150 mg SC arm, 12.4% [11/89] in the SEK 300 mg SC group, 12.5% [23/184] in the SEK 10 mg/kg-75 mg arm and 24.3% [43/177] in the SEK 10 mg/kg-150 mg arm). In addition, 7 SEK treated patients (including 4 in the IV SEK dose regimens versus 3 in the PBO group) developed ALT readings 3-5 x ULN and another 2 SEK treated patients (including 1 in each IV SEK loading arm) recorded ALT elevations that were >5 x ULN (versus 1 subject in the PBO group).

Elevations in serum AST readings followed a similar pattern. By 16 weeks, the incidence of raised AST values was 12.4% (36/290) in the PBO group versus 13.0% (86/664) in the combined SEK treatment population (11.7% [11/94] in the SEK 75 mg SC group, 17.6% [16/91] in the SEK 150 mg SC arm, 11.6% [11/95] in the SEK 300 mg SC group, 12.7% [25/197] in the SEK 10 mg/kg-75 mg group and 12.3% [23/187] in the SEK 10 mg/kg-150 mg arm). In addition, 4 SEK treated patients (including 2 the IV SEK dose regimens versus 2 in the PBO group) developed AST readings 3-5 x ULN and another SEK treated patient (treated with SEK 10 mg/kg-75 mg SC injections) recorded AST elevations that were >5 x ULN (versus 1 in the PBO group).

A small proportion of subjects developed grade 2 (1.5-3.0 x ULN) increases in serum total bilirubin (1.0% [7/700] in the pooled SEK treatment cohort versus 0.3% [1/299] in the PBO group), but no subject developed clinically significant increases in serum total bilirubin (grade 3 or higher).

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 phase 3 psa studies, the incidence of raised serum transaminases was numerically highest in the SEK 150 mg group versus the 2 other SEK doses (75 mg and 300 mg). The incidence of raised ALT values was 28.8% (111/385) in the SEK 150 mg group compared with 24.1% (86/357) in the SEK 75 mg arm and 18.3% (24/131) in the SEK 300 mg dose cohort. Similarly, the incidence of raised AST values was highest in the SEK 150 mg group at 20.4% (83/406) versus 18.4% (70/380) in the SEK 75 mg arm and 13.7% (19/139) in the SEK 300 mg group. A total of 6 patients (0.6% of 970) developed grade 3 (> 5 x ULN) elevations in serum transaminases during the entire treatment period. No patient developed the combined abnormalities of serum transaminases >3×ULN with total bilirubin >2×ULN (i.e. Hy's Law laboratory criteria).

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

During the first 16 weeks, mild (grade 1) elevations in serum transaminases were seen more frequently with SEK treatment (any dose regimen) compared to PBO. By 16 weeks, the incidence of raised ALT values was 7.1% (13/184) in the PBO group versus 16.6% (61/368) in the combined SEK treatment population (19.1% [13/68] in the SEK 75 mg SC group, 20.6% [14/68] in the SEK 150 mg SC arm, 14.5% [17/117] in the SEK 10 mg/kg-75 mg group and 14.8% [17/115] in the SEK 10 mg/kg-150 mg arm). In addition, 4 patients in the IV SEK dose regimens (versus 1 in the PBO group) developed ALT readings 3-5 x ULN and another 3 SEK treated patients (including 1 in the SEK 150 mg SC dose arm) recorded ALT elevations that were >5 x ULN (versus 1 subject in the PBO group).

Elevations in serum AST readings followed a similar pattern. By 16 weeks, the incidence of raised AST values was 7.0% (13/187) in the PBO group versus 11.3% (43/379) in the combined SEK treatment population (15.7% [11/70] in the SEK 75 mg SC group, 13.0% [9/69] in the SEK 150 mg SC arm, 10.7% [13/121] in the SEK 10 mg/kg-75 mg group and 8.4% [10/119] in the SEK 10 mg/kg-150 mg arm). In addition, 2 patients in the IV SEK dose regimens (versus 0 in the PBO group) developed AST readings 3-5 x ULN and another 3 SEK treated patients (1 in the SEK 150 mg SC dose arm) recorded AST elevations that were >5 x ULN (versus 1 in the PBO group).

A small proportion of subjects developed minor (≥ x 1.5 ULN) increases in serum total bilirubin (2.3% [9/390] in the pooled SEK treatment cohort versus 1.0% [2/191] in the PBO group), but no subject developed clinically significant increases in serum total bilirubin (grade 2 or higher).

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 Phase 3 AS studies, the incidence of raised serum transaminases was numerically higher in the SEK 150 mg group versus the 75 mg arm. The incidence of raised ALT values was 28.3% (76/269) in the SEK 150 mg group and 19.8% (53/268) in the SEK 75 mg arm. The incidence of raised AST values was 16.3% (45/276) in the SEK 150 mg group versus 13.1% (36/275) in the SEK 75 mg arm. A total of 5 patients (0.9% of 571) developed grade 3 (> 5 x ULN) elevations in serum transaminases during the entire treatment period. One patient treated with SEK 75 mg injections in Study F2305 had a background history of hyperbilirubinaemia and developed the combined abnormalities of serum transaminases >3×ULN with total bilirubin >2×ULN (i.e. Hy's Law laboratory criteria). The abnormality of liver function resolved with continued SEK treatment and did not meet the clinical criteria for Hy's law.

8.5.1.2. Other studies

All SEK treatment data pool

The profile of abnormalities in liver function in the all SEK treatment data pool is comparable to that seen in PsA and AS.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

Psoriatic arthritis

In the short term period (first 16 weeks) of the 2 Phase 3 PsA studies, 0.4% (3/700) of subjects treated with SEK (any dose regimen) developed a transient grade 2 increase in serum creatinine (1.5-3.0 x ULN) compared with 0.3% (1/300) of PBO patients. There were no cases of grade 3 or 4 abnormalities of kidney function.

Over the entire treatment follow-up period of the Phase 3 PsA trials, 1.0% (10/969) of all SEK treated subjects were recorded as having a grade 2 abnormality of kidney function. Affected individuals were equally represented across the 3 SEK doses (75 mg, 150 mg and 300 mg). In addition, 1 subject treated with SEK 75 mg injections (0.3% of 390) experienced a grade 3 increase (3-6 x ULN) in serum creatinine, which was transient.

Ankylosing spondylitis

In both of the Phase 3 AS studies (initial 16 week phase plus the entire treatment period up to 52 weeks), only 1 subject developed a transient grade 2 increase in serum creatinine (1.5-3.0 x ULN). This subject received SEK 150 mg SC therapy from randomisation in Study F2310. No grade 3 or 4 events of renal impairment were observed in the Phase 3 AS program.

8.5.2.2. Other studies

All SEK treatment data pool

The profile of abnormalities in kidney function in the all SEK treatment data pool is comparable to that seen in PsA and AS.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

Psoriatic arthritis

In the initial 16-week period of both Phase 3 PsA studies, 5.7-7.0% of SEK and PBO treated subjects developed grade 2 increases in fasting serum glucose (8.9-13.9 mmol/L). In addition, 3.8-5.4% of subjects developed mild transient hypoglycaemia. Expectedly, the frequency of hyperglycaemia (10.1%) and hypoglycaemia (9.7%) increased slightly over 52 weeks of follow-up. Apart from lipid abnormalities, no other clinically significant abnormalities of clinical chemistry were observed in the short and medium term follow-up periods (up to 52 weeks of treatment follow-up).

Over the first 16 weeks of therapy in the 2 Phase 3 PsA studies, the incidence of grade 1 cholesterol elevation (>ULN-7.75 mmol/L) were higher in the pooled SEK dataset (29.6%; 117/395) compared to the PBO group (22.7%; 34/150). In addition, 1.6% (11/683) of SEK treated patients and 0.3% (1/291) of PBO treated subjects developed a higher level of serum cholesterol elevation (grade 2; between 7.75 and 10.34 mmol/L). No subjects developed elevations in cholesterol that were grade 3 or 4. Patients treated with SEK who recorded serum cholesterol elevations >ULN were equally distributed across the 5 SEK treatment groups (i.e. no dose or loading regimen affect was observed). A similar pattern was observed for the incidence of elevated fasting serum triglycerides. The overall incidence of grade 1 increases in triglyceride (1.71-3.42 mmol/L) were 28.3% (131/463) in the pooled SEK cohort and 20.8% (41/197) in the PBO group. The majority of SEK treated patients who experienced increases in fasting serum triglyceride levels were treated with SEK 150 mg therapy (36.5% [23/63] in the SC arm and 31.4% [44/140] in the IV loading regimen).

Over the entire treatment period of the Phase 3 AS studies, the incidence and pattern of dyslipidaemia remained similar to that observed in the first 16 weeks. At 52 weeks, the

incidence of grade 1 hypercholesterolaemia was 37.0% (191/516) in the pooled SEK cohort and 33.4% (207/619) for grade 1 hypertriglyceridaemia. Four patients (3 of which were treated with SEK 150 mg injections) developed grade 4 hypertriglyceridaemia (>11.4 mmol/L) at week 52.

Ankylosing spondylitis

In the initial 16-week period of both Phase 3 AS studies, 2.6-3.1% of SEK and PBO treated subjects developed grade 2 increases in fasting serum glucose (8.9-13.9 mmol/L). In addition, 1.0% of subjects developed mild transient hypoglycaemia. Apart from lipid abnormalities, no other clinically significant abnormalities of clinical chemistry were observed in the short and medium term follow-up periods (up to 52 weeks of treatment follow-up).

Over the first 16 weeks of therapy in the 2 Phase 3 AS studies, cholesterol levels ≥ULN but ≤1.5×ULN were comparable between the pooled SEK dataset (20.0%; 46/230) and the PBO group (19.8%; 23/116). Only 3 patients (all treated with SEK) developed a higher level of serum cholesterol elevation (between 1.5-2.5x ULN). No subjects developed elevations in cholesterol that were >2.5× ULN. The majority of patients (80%; 37/46) with cholesterol elevations > ULN were treated in either of the 2 IV SEK loading dose treatment groups. A similar pattern was observed for the incidence of elevated fasting serum triglycerides. The overall incidence of grade 1 increases in triglyceride (1.71-3.42 mmol/L) were 17.8% (55/309) in the pooled SEK cohort and 17.1% (25/146) in the PBO group. The majority of SEK treated patients who experienced increases in fasting serum triglyceride levels were in either of the IV loading dose arms (71%; 39/55). Over the entire treatment period of the Phase 3 AS studies, the incidence and pattern of dyslipidaemia remained similar to that observed in the first 16 weeks. One patient treated with SEK 75 mg injections developed grade 4 hypercholesterolaemia at week 52. This patient had a baseline cholesterol value of 9.99 mmol/L, which increased to 11.75 mmol/L at week 24, and then further to 13.21 mmol/L at week 52. This patient had a history of hypertension and reported an AE of palpitations. He continued on SEK injections and declined lipid-lowering therapy.

8.5.3.2. Other studies

All SEK treatment data pool

The profile of abnormalities in clinical chemistry parameters in the all SEK treatment dataset is comparable to that seen in PsA and AS.

8.5.4. Haematology

8.5.4.1. Pivotal studies

Psoriatic arthritis

Short term period (16 weeks) of phase 3 studies

In the first 16 weeks, CTCAE grades 1 and 2 neutropenia were more commonly recorded in the SEK treatment groups (2.1% [15/701] for the pooled dataset) than PBO (1.3%; 4/300). There was no clear dose-effect relationship between SEK and grade 1-2 neutropenia. The incidence of grade 1-2 neutropenia (1.0-1.5 x 10^9/L) was 2.0% (2/99) in the SEK 75 mg SC group, 1.0% (1/99) in the SEK 150 mg SC arm, 4.0% (4/99) in the SEK 300 mg SC group, 3.0% (6/202) in the SEK 10 mg/kg-75 mg arm and 1.0% (2/202) in the SEK 10 mg/kg-150 mg group. There were also 3 cases of grade 3 neutropenia (0.5-1.0 x 10^9/L), which occurred in 2 patients (1.0% of 202) in the SEK 10 mg/kg-150 mg group and 1 subject (1.0% of 99) in the SEK 300 mg SC arm. None of these 3 subjects developed infection. One PBO treated subject developed grade 3 thrombocytopenia (25-50 x 10^9/L) and 4 SEK treated patients (0.6% of 702) experienced grade 2 thrombocytopenia (50-75 x 10^9/L).

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 Phase 3 PsA studies, the incidence of newly occurring or worsening abnormalities in haematology parameters remained low and no dose dependent effect with SEK SC therapy was observed. The overall incidence of grade 2 neutropenia at 52 weeks was 4.1% (40/970), which occurred at a similar frequency in each of the 3 SEK dose groups (3.8-4.3%). Four patients developed grade 3 neutropenia (0.5-1.0 x 10^9/L), including 1 additional case (treated with SEK 75 mg injections) identified after the initial 16-week treatment period. A total of 4 SEK treated subjects (incidence of 0.4%; 4/971) developed grade 2 thrombocytopenia (50-75 x 10^9/L) in the entire treatment period of the Phase 3 AS studies.

Ankylosing spondylitis

Short term period (16 weeks) of phase 3 studies

Nearly all of the newly occurring or worsening abnormalities in haematology parameters during the initial 16 week treatment period of the Phase 3 AS studies were CTCAE grade 1 or 2. The only CTCAE grade 3 haematological abnormalities were 2 cases of anaemia (haemoglobin <80 g/L), which involved 1 case each from the PBO and SEK 10 mg/kg-75 mg group. Furthermore, the majority (>80%) of all other haematology abnormalities were reported in the 2 IV SEK loading dose groups. In particular, the incidence of grade 1-2 neutropenia (1.0-1.5 x 10^9/L) was 3.3% (4/123) in the SEK 10 mg/kg-75 mg group, 2.4% (3/124) in the SEK 10 mg/kg-150 mg arm and 1.4% (1/73) in the SEK 75 mg SC group versus 0 in the PBO and SEK 150 mg SC groups. There was only 1 case of grade 2 thrombocytopenia (50-75 x 10^9/L), which occurred in a patient in the SEK 10 mg/kg-150 mg treatment group.

Entire treatment period of phase 3 studies

Over the entire treatment period of the 2 Phase 3 AS studies, the incidence of newly occurring or worsening abnormalities in haematology parameters remained low and no dose dependent effect for SEK 75 mg injections versus 150 mg therapy was observed. All but 2 of the additional haematological abnormalities were CTCAE grade 1 or 2. One patient treated with SEK 75 mg injections in Study F2305 developed grade 4 neutropenia (<0.5 x 10^9/L), which was not associated with any other AEs and did not result in treatment discontinuation (overall incidence of 0.2% [1/569] in the total pooled SEK cohort). Grade 3 neutropenia (0.5-1.0 x 10^9/L) affected a total of 4 SEK treated subjects (incidence of 0.7%; 4/569) – 3 subjects received 75 mg injections and 1 received SEK 150 mg therapy. One patient treated with SEK 75 mg also developed grade 3 lymphopenia (0.2-0.5 x 10^9/L). There were no additional cases of grade 2 or higher thrombocytopenia in the entire treatment period of the Phase 3 AS studies.

8.5.4.2. Other studies

All SEK treatment data pool

The profile of abnormalities in haematology parameters in the all SEK treatment dataset is comparable to that seen in PsA and AS.

8.5.5. Immunogenicity

8.5.5.1. Pivotal studies

The development of SEK specific anti-drug antibodies (ADA) and neutralising antibodies were assessed using a validated assay in all of the Phase 2 and 3 clinical trials for both proposed treatment indications. Immunogenicity samples for the analysis of ADA were collected before study treatment at baseline and immediately before dosing at weeks 16, 24 and 52 in all of the Phase 3 trials. In the Phase 3 studies, samples were analysed using a Meso Scale Discovery (MSD) bridging assay with a stepwise approach for screening, confirmation and titration. Confirmed positive samples were then assessed for neutralising antibodies. The ADA assay sensitivity was 4 ng/mL with drug tolerance measured at 53.8 µg/mL using 250 µg/mL of rabbit

polyclonal positive control antibody. In the Phase 2 trials, immunogenicity samples were analysed with a Biacore assay.

Psoriatic arthritis

In the Phase 3 PsA studies, 1.6% (16/996) of patients were ADA positive at baseline, but 10 of those subjects subsequently reverted to being ADA negative once they received SEK treatment. Six subjects treated with SEK had persistently positive ADA from baseline that did not change in quantity or type over time. In this subset of subjects, the detection of ADA was intermittent and of low titre. Only 1 patient (0.1% of 996 – 599 patients in Study F2306 and 397 subjects in Study F2312) developed treatment emergent ADA to SEK at week 24, which was also neutralising. This subject was classified as a PBO non-responder at week 16 in Study F2306 and then was re-randomised to SEK 75 mg SC injections. The presence or development of ADA was not associated with AEs or loss of efficacy in the 16 subjects with positive ADA in both Phase 3 PsA trials.

Ankylosing spondylitis

In the Phase 3 AS studies, 1.4% (8/584) of patients were ADA positive at baseline, but 7 of those subjects subsequently reverted to being ADA negative once they received SEK treatment. One subject treated with SEK had persistently positive ADA from baseline that did not change in quantity or type over time. Only 2 patients (0.3% of 584 – 364 patients in Study F2305 and 220 subjects in Study F2310) developed treatment emergent ADA to SEK at week 52, 1 of which was neutralising. The development of ADA was not associated with AEs or loss of efficacy in these 2 subjects.

8.5.5.2. Other studies

All SEK treatment data pool

Nil new information on this issue was available for the SEK treatment data pool.

8.5.6. Electrocardiograph

8.5.6.1. Pivotal studies

Psoriatic arthritis

In the first 16 weeks of the 2 Phase 3 PsA studies, 2 patients developed a newly occurring prolongation in QT interval to ≥500 msec. One patient received treatment with IV SEK in Study F2306 and then SC 150 mg injections thereafter, and the other subjects was in the PBO arm of Study F2312. Both subjects had a significant prior history of complex cardiac disease. Neither of the subjects ceased treatment. The patient treated with SEK subsequently recorded an SAE of coronary artery disease and worsening cardiac failure on study day 348. Over the entire treatment period of the 2 Phase PsA studies, one additional patient (treated initially with PBO and then SEK 75 mg SC injections from week 16 in Study F2306 because of non-response) developed worsening of pre-existing QT prolongation at week 52 (increased from 482 msec to 529 msec), which was reported as a non-serious AE. No other clinically significant ECG abnormalities between any of the treatment groups (SEK versus PBO in the first 16 weeks; and any dose of SEK in the entire treatment period) were observed in the Phase 3 PsA studies.

Ankylosing spondylitis

In the first 16 weeks and the entire treatment period of the 2 Phase 3 AS studies, there were no clinically meaningful differences in ECG abnormalities between any of the treatment groups (SEK versus PBO in the first 16 weeks; and any dose of SEK in the entire treatment period). In particular, no subjects were recorded as developing a prolongation in QT interval ≥500 msec.

8.5.6.2. Other studies

All SEK treatment data pool

No new safety concerns

8.5.7. Vital signs

8.5.7.1. Pivotal studies

Psoriatic arthritis

New onset, clinically significant abnormalities in vital signs during the first 16 weeks of treatment in the 2 Phase 3 PsA trials were reported at comparable rates across the 5 SEK dose groups and the PBO arm. For example, the frequency of newly occurring increases in sitting systolic blood pressure was 26.5% (157/593) in the pooled SEK treatment cohort and 25.8% (60/233) in the PBO group. The incidence of decreased systolic blood pressure (≤1%), as well as high (≤5%) or low (13.5%) pulse rates were lower than the raised systolic blood pressure incidence, but comparable across all treatment groups. Over the entire treatment period in the 2 Phase 3 PsA studies, the profile of blood pressure and pulse rate abnormalities was similar to that observed in the first 16 weeks, with the expected slight increase in frequency for each parameter over the longer exposure period (e.g. the frequency of raised systolic blood pressure rose to 35%).

Ankylosing spondylitis

In the first 16 weeks and the entire treatment period of the 2 Phase 3 AS studies, there were no clinically significant treatment differences in blood pressure (high or low readings; systolic or diastolic blood pressure) or pulse rate with SEK.

8.5.7.2. Other studies

All SEK treatment data pool

No new safety concerns.

8.6. Post-marketing experience

At the time of submission, SEK has not been registered anywhere in the world for use in either PsA or AS. Hence, the sponsor has not provided any post-marketing dataset.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

SEK therapy appears to be associated with a slightly higher frequency of elevated serum transaminases compared to PBO in the first 16 weeks of therapy in both treatment indications. There does appear to be a consistent dose related relationship between raised serum AST and/or ALT with SEK therapy. The abnormalities of liver function often resolved with continued SEK treatment and none meet the clinical criteria for Hy's law. Further details regarding abnormal liver function tests are presented.

8.7.2. Haematological toxicity

In the PSOR safety dataset, drug related neutropenia was an identified safety risk with SEK. Based on central laboratory analyses in the Phase 3 PSOR trials, the incidence of grade 2 neutropenia (1.0-1.5 x 10^9/L) in the first 12 weeks was higher with SEK treatment (1.6-1.7% for both 150 mg and 300 mg therapy) compared with PBO (0.3%). Over the extended treatment follow-up period in the PSOR dataset, the annual incidence of grade 2 or higher neutropenia was 2.5%, with no dose response relationship being observed.

In the short term period (first 16 weeks) of both pivotal Phase 3 programs (PsA and AS), the overall incidence of neutropenia was higher in the SEK treated population compared with PBO therapy. The approximate overall incidences of neutropenia were 2.0-4.0% for SEK (with a dose response relationship observed for 75 mg, 150 mg and 300 mg therapy) versus 1.3% for PBO in the PsA studies; and 2.0% for SEK (pooled result; no dose difference) versus 0 for PBO in the 2 pivotal Phase 3 AS trials. In the short term follow-up phase of the PsA studies, there were 3 cases of grade 3 neutropenia (0.5-1.0 x 10^9/L), including 1 case in each of the 3 SEK dose groups. No cases of grade 3 or 4 neutropenia were observed in the AS program. The majority of neutropenic episodes were transient and not associated with infection related AEs.

Over the entire treatment period of the Phase 3 PsA studies, the incidence of grade neutropenia was 3.8-4.3% with SEK (dose independent) and the incidence of grade 3 neutropenia was 0.5% (slightly higher in the 300 mg group at 0.7% versus 0.3% in the SEK 75 mg dose group). Over the entire treatment period of the Phase 3 AS studies, the incidence of grade 3 neutropenia was higher in the SEK 75 mg group at 3.5% versus 1.7% in the SEK 150 mg arm. The incidence of grade 3 neutropenia was also slightly higher in the SEK 75 mg dose group at 1.1% (3 cases) compared to 0.3% (1 case) in the SEK 150 mg arm. Like the week 16 data, most episodes of neutropenia were transient and not associated with infection; although 1 neutropenic patient treated with SEK in the AS dataset developed a non-serious URTI.

8.7.3. Risk of infection

Because SEK is an immunomodulatory therapy, there is biological plausibility for an increased risk of overall infection, as well as an increased risk of certain types of infections (e.g. Candida) and potentially encapsulated bacteria. The 12-week PSOR dataset showed an increased incidence of overall infection with both the 150 mg and 300 mg doses of SEK (28-29%) compared with PBO (19%). Candida infections were also more frequently reported with SEK (in a dose dependent manner). The extended treatment dataset in PSOR subjects showed a small increase in exposure adjusted infection rates with SEK 300 mg therapy versus 150 mg injections, and this was also observed for some specific infections (notably, Candida and oral herpes infections).

In the short term period (first 16 weeks) of both pivotal Phase 3 programs (PsA and AS), the overall incidence of infection is higher in the SEK treated population compared with PBO therapy. The approximate overall incidences of infection were 30% for SEK (pooled) versus 25% for PBO in the PsA studies; and 31% for SEK (pooled) versus 18% for PBO in the 2 pivotal Phase 3 AS trials. In the short term follow-up phase of the PsA studies, the overall incidence of infection was similar in the 2 higher SEK dose groups (29-30% for 150 mg and 300 mg) but lower in the SEK 75 mg dose cohort (23%). In the AS program where only the 2 lower doses of SEK were evaluated in the Phase 3 studies, the overall incidence of infection was similar in the 75 mg and 150 mg dose groups (30% versus 33%, respectively). The majority of infections in both treatment indications were URTI and nasopharyngitis. However, 5 cases of Candida infection were reported in SEK treated patients in the PsA 16-week dataset, and 2 SEK treated cases were observed in the short term AS cohort (versus zero cases in the PBO group of both indications). The majority of Candida infections involved the oral cavity but there were reports of oesophageal (in 1 patient treated with 300 mg injections) and genital involvement (2 subjects). All cases of Candida infection were non-serious, resolved with antifungal treatment and did not result in permanent discontinuation from SEK. In both treatment indications, there were no other cases of opportunistic infection such as reactivated latent TB in the short term follow-up period (up to 16 weeks).

Over the entire treatment period of the Phase 3 PsA studies, the exposure adjusted incidence of infection was dose dependent for SEK. The incidence of overall infection was highest in the SEK 300 mg dose group (95 infections per 100 PY) compared to 89 infections per 100 PY in the SEK 150 mg injection cohort and 72 infections per 100 PY in the SEK 75 mg dose group. Respiratory tract infections remained the most common type of infection, but there were 10 additional cases

of Candida infection (i.e. 15 in total for the PsA dataset) in the entire treatment period. The majority of these cases were oral candidiasis (1 serious), but 3 of the AEs were oesophageal candidiasis. Over the entire treatment period of the Phase 3 AS studies, the exposure adjusted incidence of infection was similar for both examined doses of SEK. The incidence of overall infection was 68 infections per 100 PY in the SEK 75 mg dose group and 68 infections per 100 PY in the SEK 150 mg arm. Like the PsA data, respiratory tract infections remained the most frequent type of infection over time, but there were 4 additional cases of Candida infection (i.e. 6 in total for the AS dataset) in the entire treatment period. Another subject treated with SEK 75 mg injections also experienced an opportunistic infection of disseminated cutaneous herpes zoster.

8.7.4. Cardiovascular safety

Several studies indicate that adult patients with PsA or AS have an increased risk of cardiovascular disease, at least partly explained by chronic systemic inflammation. In addition, published data suggests that IL-17 has a role in vascular inflammation and atherosclerosis. SEK may affect lipid profiles and control of systemic inflammation may potentially reduce the risk of MACE. Over the entire treatment period of the PSOR dataset, there was a very low incidence of MACE (5 events in the SEK 150 mg dose group and 6 events in the SEK 300 mg cohort versus 1 PBO subject suffered a brain stem haemorrhage).

Over the entire treatment period of the Phase 3 PsA studies, the exposure adjusted incidence of MACE was highest in the SEK 75 mg dose group (1.7 events per 100 PY; 7 patients) compared to 0.2 events per 100 PY in the SEK 150 mg injection cohort (1 case) and no cases in the PBO and SEK 300 mg dose groups. All MACE cases were reported as SAEs and occurred in subjects with a prior history of cardiovascular disease or 2 or more active risk factors for cardiovascular events. Over the entire treatment period of the Phase 3 AS studies, there were 4 MACE cases (2 in each SEK dose group) resulting in an exposure adjusted incidence of MACE of 0.6 events per 100 PY for SEK 75 mg and 150 mg therapy. All MACE cases in the AS dataset were reported as SAEs and occurred in high risk individuals.

8.7.5. Unwanted immunological events

Across the Phase 3 study program for both indications, the incidence of new treatment emergent ADA to SEK by 52 weeks of therapy was very low at 0.1% (1/996) in the PsA cohort and 0.3% (2/584) in the AS population. In the PSOR treatment dataset, the corresponding incidence of ADA was slightly higher at 0.7%, but still very low for a monoclonal antibody therapy. In both the PsA and AS populations, the sponsor examined for the potential impact of the presence of ADA (both treatment emergent and overall presence, including positive ADA at baseline) on efficacy, PK parameters and possible immune related AEs, such as hypersensitivity reactions. In both treatment datasets, there was no correlation between altered PK, loss of efficacy and immune related AEs, which is reassuring given the overall small number of subjects with positive ADA results.

In the PSOR dataset, hypersensitivity AEs were reported more commonly in patients treated with SEK (4.5% incidence at week 12) than with PBO (1.3%). The difference was primarily driven by reports of urticaria and eczema. One PSOR patient receiving treatment with SEK 150 mg injections experienced anaphylaxis, confounded by a history of nut allergy. There were also 2 reports of possible angioedema in the PSOR population. Both the PsA and AS datasets included in this submission showed a low and consistent incidence of reported hypersensitivity AEs which was mainly accounted for by urticaria, non-specific rash and dermatitis (each reported at ≤1.5% incidence in the first 16 weeks and ≤2% over the entire treatment period). In the short term PsA cohort, there was 1 case report of treatment related, moderately severe angioedema in a patient receiving SEK 75 mg injections (after IV loading) that required discontinuation from SEK (patient recovered).

In both the PsA and AS populations, there was a low incidence of Crohn's disease reported as AEs, which may reflect either an aggravation of an associated autoimmune bowel condition in at-risk population and/or the background incidence of the associated co-morbidity. The current dataset remains unclear on this issue but ongoing surveillance for this potential risk with SEK is recommended.

8.8. Other safety issues

8.8.1. Safety in special populations

For both treatment indications, the sponsor has conducted an analysis of the safety data according to various subgroups based on demographic and co-morbid factors. The subgroup analyses included age (<65 years, ≥65 years), gender, race, subject weight (<70 kg, 70-90 kg, >90 kg) and 10-year risk category of coronary heart disease (high >20%, medium 10-20%, low <10%). Some of the subgroups were too small in number (e.g. only 24 patients [15 of whom were treated with SEK] were aged >65 years in the 2 pivotal Phase 3 studies)[11] to make reliable data interpretations; however, none of the factors appeared to significantly influence the exposure adjusted incidence rate or type of AEs, apart from high subject weight (>90 kg) being associated with a higher overall incidence of AEs, which was primarily explained by a higher incidence of infection. The concomitant use of MTX and/or oral CS did not have an impact on the incidence or type of AEs, including the risk of infection.

There is insufficient clinical data from the use of SEK in pregnant or lactating women to adequately assess the safety of SEK use during pregnancy or lactation. Animal studies do not suggest any direct or indirect harmful effects with SEK regarding pregnancy, foetal development or parturition.

8.8.2. Safety related to drug-drug interactions and other interactions

Live vaccines should not be given concurrently with SEK. Patients were excluded from the Phase 2 and 3 studies in PsA and AS if they planned to receive any live vaccine during the study period or 6 weeks prior to randomisation. A vaccine sub-study (A2224) was provided in the original SEK submission. Meningococcal and inactivated influenza vaccinations were given to healthy volunteers and a similar proportion of SEK and PBO treated subjects were able to mount an adequate immune response of at least a 4-fold increase in antibody titre. This data suggests that SEK does not impair humoral immune responses to meningococcal and influenza vaccines.

No specific drug-drug interaction studies with SEK have been conducted in humans. SEK has been concurrently administered with MTX, CS and NSAID drugs to moderately large numbers of adult patients with active PsA or AS. There does not appear to be an increased risk of AEs or significant alteration in efficacy when SEK is concomitantly administered with any of these co-therapies.

8.9. Evaluator's overall conclusions on clinical safety

In this submission, the total clinical safety dataset for the use of SEK in adult patients with active PsA consists of 974 patients treated with SEK in 2 pivotal Phase 3 studies (F2306 and F2312) providing 955 PY of exposure, and 1 supporting Phase 2 trial (A2206) supplemented with additional safety information from patients in the PSOR studies who had concomitant PsA (an additional 498 SEK treated subjects with 360 PY of exposure. In the pivotal Phase 3 studies, the median duration of exposure to SEK was 48 weeks. In the PsA program, SEK therapy was given by SC injection either at a dose of 75mg, 150 mg or 300 mg. Both of the proposed doses in PsA (150 mg and 300 mg) had more than 300 subjects exposed to SEK for at least 6 months.

[11] This number is for AS.

Approximately half of the patients in the PsA dataset received concurrent MTX, more than 75% were taking concomitant NSAID, and approximately one sixth were taking concurrent low dose oral CS. In the PsA trials, almost one third of all subjects had received prior biologic therapy with anti-TNF drugs. Overall, there is a sufficient volume of data to make a meaningful assessment of SEK safety for up to 52 weeks of treatment in the newly proposed treatment indication of active PsA.

In this submission, the total clinical safety dataset for the use of SEK in adult patients with active AS consists of 571 patients treated with SEK in 2 pivotal Phase 3 studies (F2305 and F2310) providing 691.1 PY of exposure, and 1 supporting Phase 2 trial (A2209) supplemented with additional safety information from patients with various other autoimmune conditions who received SEK in other studies. In the pivotal Phase 3 studies, the majority of patients (78%) received SEK for at least 52 weeks and 28% of all subjects have been treated for at leats 76 weeks. In the AS program, SEK therapy was given by SC injection either at a dose of 75mg or 150 mg. The proposed maintenance dose in AS is 150 mg every 4 weeks, for which more than 300 subjects exposed to SEK for at least 6 months (i.e. the minimum regulatory guideline requirement). Approximately half of the patients in the AS dataset were taking concomitant NSAID and almost one third of all subjects had received prior anti-TNF therapy. Overall, there is a sufficient volume of data to make a meaningful assessment of SEK safety for up to 76 weeks of treatment in the proposed treatment indication of active AS.

The safety findings for both newly proposed treatment indications (PsA and AS) are highly similar for the incidence and pattern of AEs, therefore will be considered together in this summary. Moreover, the incidence and profile of AEs observed in the 2 new datasets is highly similar to that reported in the current approved treatment indication of PSOR. No new safety concerns with SEK have been identified in the current submissions.

Infection was the most common AE recognised with SEK in both treatment datasets and these occurred at a higher frequency in the SEK treatment groups versus control during the PBO-controlled treatment periods (16 weeks for both treatment indications). The majority of infections were mild in severity, self-limiting, and were predominately either nasopharyngitis or URTI. The use of concurrent MTX or prior exposure to anti-TNF therapies did not appear to increase the overall risk of AEs, including infection related AEs. However, subject weight >100 kg was associated with a higher incidence of overall and infection related AEs. SAEs including serious infection related events were reported in a low proportion of SEK-treated patients in both treatment indications (<3.0 serious infections per 100 PY of exposure). No patients developed reactivation of latent tuberculosis. However, consistent with the PSOR clinical development program, there was an increased risk of localised (non-invasive) Candida infections with SEK in both treatment indications as well as increased rates of herpes viral infections (mainly, oral or genital in location). This finding may be expected given the role of IL-17A in protective immunity, particularly against fungal infections. A SEK dose effect was frequently observed for the risk of candidiasis. The majority of Candida infections were rated as mild or moderate in severity, responded to standard anti-fungal treatment and did not result in permanent discontinuation from SEK.

Hypersensitivity reactions were an uncommon type of AE reported at a similar or slightly higher incidence in patients receiving SEK (with no dose response relationship) compared to PBO therapy. Most hypersensitivity AEs were non-specific reports of rash, dermatitis and urticaria, which were rated as mild in severity, resolved without specific intervention and did not result in discontinuation from SEK. Only 1 potential systemic hypersensitivity reaction was reported with SEK in the PSA safety dataset. Discontinuations due to AEs occurred at a low and similar frequency in SEK versus PBO treated subjects. Consistent with PSOR study findings, cases of inflammatory bowel disease (mainly, Crohn's disease) were reported across the PsA and AS studies (either new onset or exacerbation of pre-existing disease). Some of the cases

were also reported in PBO-treated subjects and the direct causal relationship between Crohn's disease and SEK therapy is unclear.

A total of 2 deaths have been reported in patients with PsA up to 52 weeks of treatment, including 1 death due to intracranial haemorrhage in a patient treated with SEK 75 mg injections in Study F2306 and the other fatality occurred in a patient with PSOR and concomitant PsA who received SEK 300 mg SC injections following PBO in a Phase 3 PSOR trial. In the AS safety dataset, a total of 3 deaths occurred in the pivotal Phase 3 studies (2 treated with SEK 75 mg therapy [acute myocardial infarction and respiratory failure] and 1 received PBO, who committed suicide). A total of 8 patients (all treated with SEK; 7 of which received 75 mg injections) in the PsA dataset and 4 subjects (all treated with SEK; 2 each in the 75 mg and 150 mg dose groups) in the AS program recorded MACE in the extended follow-up period of up to 60 weeks duration. Across the 2 treatment indications, the MACE episodes included 6 cases each of myocardial infarction and various types of cerebrovascular accident. All of the patients had significant cardiovascular disease risk factor profiles for suffering MACE and the relationship between these types of AEs and SEK remains unclear as the exposure adjusted incidence rate of MACE with SEK therapy in both treatment indications (0.73 per 100 PY in the overall PsA cohort and 0.43 per 100 PY in the AS population) is comparable to the published rate of MACE in the matched populations (0.57 per 100 PY for both indications). Three patients developed malignancies in the PsA studies, which included 2 reports of non-melanoma skin cancer and 1 case of intraductal breast cancer. In the AS population, there were 5 reports of malignancy which included 2 cases of B-cell lymphoma and 3 individual reports of malignant melanoma, breast cancer and bladder carcinoma. The total safety dataset thus far (including the PSOR experience) does not suggest an increased risk of malignancy with SEK over PBO in matched patients. However, longer periods of treatment follow-up are required to inform about this potential safety signal.

Neutropenia is a recognised safety concern with SEK, which was identified in the PSOR studies. In the short term period (first 16 weeks) of both pivotal Phase 3 programs (PsA and AS), the overall incidence of neutropenia was higher in the SEK treated population compared with PBO therapy. The approximate overall incidences of neutropenia were 2.0-4.0% for SEK (with a dose response relationship observed for 75 mg, 150 mg and 300 mg therapy) versus 1.3% for PBO in the PsA studies; and 2.0% for SEK (pooled result; no dose difference) versus 0 for PBO in the 2 pivotal Phase 3 AS trials. In the short term follow-up phase of the PsA studies, there were 3 cases of grade 3 neutropenia (0.5-1.0 x 10^9/L), including 1 case in each of the 3 SEK dose groups. No cases of grade 3 or 4 neutropenia were observed in the AS program. Over the entire treatment period of the Phase 3 PsA studies, the incidence of grade neutropenia was 3.8-4.3% with SEK (dose independent) and the incidence of grade 3 neutropenia was 0.5% (slightly higher in the 300 mg group at 0.7% versus 0.3% in the SEK 75 mg dose group). Over the entire treatment period of the Phase 3 AS studies, the incidence of grade 3 neutropenia was higher in the SEK 75 mg group at 3.5% versus 1.7% in the SEK 150 mg arm. The incidence of grade 3 neutropenia was also slightly higher in the SEK 75 mg dose group at 1.1% (3 cases) compared to 0.3% (1 case) in the SEK 150 mg arm. The majority of neutropenic episodes were transient and not associated with infection related AEs. There were also a few cases of significant thrombocytopenia observed in patients treated with SEK (mainly in the PsA studies) and mild-moderate, asymptomatic lymphopenia has also been observed in association with SEK.

The total safety dataset also identified 2 other abnormalities of laboratory values which occurred at a numerically higher frequency in the SEK treatment cohorts compared with PBO. In both the PsA and AS study programs, elevations in hepatic transaminases and dyslipidaemia have been associated with SEK versus PBO. No dose response relationship with SEK was apparent for these 2 abnormal laboratory findings. In general, patients who developed increases in liver function tests had changes of mild-moderate severity which were transient in nature and without associated clinical sequelae.

The incidence of PsA or AS subjects developing new anti-drug antibodies to SEK is very low at ≤0.3% at 52 weeks using the combined SEK treated datasets in the pivotal PsA and AS studies, and their clinical relevance for safety outcomes is yet to be defined with no discernible link to the risk of infection, or injection related reactions.

In summary, the safety data indicates that SEK has an acceptable overall safety profile up to 52 weeks of therapy in the treatment of adult patients with moderately to severely active PsA or AS. There is limited long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and MACE, which will require additional longitudinal safety follow-up. There are some significant identified safety concerns including the risk of infection, opportunistic infection (mainly Candida and herpes infection), potential hypersensitivity related reactions, exacerbation of inflammatory bowel disease and neutropenia. These safety concerns are consistent with the known profile of SEK in the approved indication of PSOR. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for opportunistic infections, MACE and malignancy (particularly, non-melanoma skin cancers).

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of SEK in adult patients with moderately to severely active PsA in the proposed usage (150 mg injections given by SC injection; initial weekly loading regimen followed by every 4 weeks in the maintenance phase; 300 mg dose recommended in patients who are anti TNF-IR or have concomitant moderate to severe PSOR) are:

- Improvement in the signs and symptoms of peripheral arthritis (as per the ACR clinical response criteria), which appear to be maintained to at least 52 weeks of treatment.
- Improvement in physical functioning (as evidenced by treatment related improvements in the HAQ-DI scale).
- SEK therapy is associated with a lower rate of structural disease progression at 24 and 52 weeks of treatment as measured by serial plain X-rays of the peripheral joints affected by PsA.
- Concurrent use of MTX with SEK did not significantly impact upon the efficacy outcomes (for example, ACR20 response rate at 24 weeks).
- In the anti TNF-IR population of subjects in Study F2312, a statistically higher rate of ACR20 response at 24 weeks was only demonstrated with SEK 300 mg therapy.
- The benefits demonstrated with SEK versus PBO extended to various patient subgroups (age, gender, race, region and baseline disease severity) although subject weight >100 kg was associated with lower ACR response rates.
- In addition to the musculoskeletal features of PsA, SEK is an effective therapy for associated skin psoriasis if present and results in improvements in health related quality of life outcomes.
- Convenient dosing schedule (every 4 weeks in the maintenance phase of therapy) using a convenient mode of administration (SC injection via prefilled syringe or autoinjector device).

The benefits of SEK in adult patients with moderately to severely active AS in the proposed usage (150 mg injections given by SC injection; initial weekly loading regimen followed by every 4 weeks in the maintenance phase) are:

- Rates of ASAS20 response of 61% at 16 weeks of treatment, which is comparable to that seen with anti TNF therapy (treatment related difference of 33% compared with PBO).
- Rates of ASAS40 response of 36% at 16 weeks of treatment, which is comparable to that observed with anti TNF therapy (treatment related difference of 25% compared with PBO).
- Rates of ASAS20 and ASAS40 response with SEK are ~15% higher in anti TNF naïve subjects versus anti TNF-IR patients, which is an expected observation from other active therapies.
- Treatment related benefit with SEK (versus PBO) is seen across all subject weight categories, but subjects weighing >90 kg have a diminished response to treatment than subjects weighing <90 kg. This is a common finding with other drug therapies (including anti TNF drugs) in AS.
- SEK treatment produces reductions in serum inflammation (CRP) and improves disease activity (as measured by changes from baseline in the BASDAI score) over 16-52 weeks of follow-up.
- SEK treatment results in clinically meaningful improvements in health related QOL for AS patients (as measured by changes from baseline in the SF36-PCS and ASQoL scores).
- SEK appears to reduce radiographic inflammation of the spine and SI joints at 24 weeks, which offers the potential of less structural progression of AS over time (however, additional long term data is required before making any definitive conclusions).
- SEK results in improvements in health related quality of life outcomes in patients with active AS.
- Clinical improvements with SEK are maintained for at least 52 weeks of treatment follow-up.

9.2. First round assessment of risks

The risks of SEK in the proposed usage (for both treatment indications) are similar and include:

- Increased incidence of infection, which are usually minor in severity (in particular, URTI and nasopharyngitis) compared to PBO therapy.
- Increased risk of localised (non-invasive) Candida and oral herpes infection.
- Increased risk of drug induced neutropenia compared to PBO.
- Risk of precipitation and aggravation of inflammatory bowel disease, which is a common co-morbidity affecting ~5-10% prevalence in patients with PsA or AS.
- Increased frequency of raised serum transaminases and atherogenic serum lipid profiles compared to PBO.
- Potential increased risk of malignancy (particularly, non melanoma skin cancers) and MACE requiring long term surveillance – not evident in the short-medium term safety dataset.
- Live vaccines cannot be given concurrently with SEK.
- SEK has not been studied in patients <18 years of age, in subjects with significant organ dysfunction (including renal, hepatic or cardiac failure) and in pregnant or lactating women.

9.3. First round assessment of benefit-risk balance

9.3.1. Psoriatic arthritis

The overall benefit-risk balance of SEK in adult patients with moderately-severely active PsA is favourable. Although there are several new therapies approved for the treatment of PsA, a significant proportion of patients still do not achieve optimal or adequate efficacy when one considers clinically meaningful measures such as ACR20 (at least 40%) and ACR50 response (at least 50%). Other limitations to currently available therapies in Australia include slow onset of action, diminished efficacy over time and drug specific safety concerns such as opportunistic infection (including TB), malignancy (for example, lymphoma) and various laboratory test abnormalities (for example, abnormal liver function tests and cytopenia). Thus, there remains a significant unmet need for new drugs with unique mechanisms that can provide a rapid onset of effect, improved and sustained symptom improvement and a safety profile that allows for long term use.

SEK is a fully human IgG1 monoclonal antibody that selectively binds to and neutralizes the pro-inflammatory cytokine, IL-17A. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of PsA and PSOR. In this submission, SEK has been evaluated in a large clinical program which complied with CHMP guidelines for evaluation of treatments in PsA. The clinical studies evaluated an adequate number of subjects in the target patient population and demonstrated that SEK is an efficacious treatment in active PsA. For most patients with PsA, the minimum most effective dose of SEK was 150 mg injections, however the 300 mg dose was showed superior efficacy in selected subgroups (that is, those with a history of anti TNF-IR and in those with concomitant moderately severe PSOR). The superior efficacy of SEK versus PBO was consistent in most subgroups, including those taking concomitant MTX or not. Subjects with a baseline body weight >100 kg appeared to have better clinical response to the higher dose of SEK (300 mg injections) but the sponsor has not requested a dose modification in this patient subgroup.

The risk profile of SEK is based on a total of 974 SEK treated patients with PsA involved in the 2 pivotal Phase III studies as well as additional safety information collected from >4000 patients treated with any dose of SEK across a variety of autoimmune diseases. In the PsA clinical program, there was no evidence of an imbalance of SAEs with SEK compared to PBO. There was an increased incidence in overall infections in the SEK dose groups compared to PBO, with a slightly increased frequency of infection with the highest dose of SEK (300 mg therapy). The majority of reported infections were mild or moderate, upper respiratory tract infections. Candida infections were also more frequent with SEK (in a dose dependent relationship) compared to PBO. Most Candida infections were localised mucosal events, consistent with the drug mechanism of action. There was also an increased frequency of herpes infection (mainly, oral or genital) with SEK treatment. A few serious opportunistic infections, such as disseminated cutaneous herpes zoster, were reported with SEK. However, this is included in the proposed PI. No tuberculosis or viral hepatitis reactivation was observed in any PsA trial.

Neutropenia was more frequently observed with SEK than placebo, but most cases were of mild severity (CTCAE grade 1-2), transient and reversible. More severe neutropenia (CTCAE grade 3) was also infrequently observed with SEK, but was not associated with an increase in infection. There was a small increase in incidence of mild hepatic transaminase elevations and dyslipidaemia with SEK versus PBO, which was not clearly dose related.

Malignancy represents a theoretical risk with any immunosuppressive therapy, but there is no evidence that SEK confers an increased risk for malignancy in the current dataset of medium drug exposure. Due to the potential involvement of the IL-17 pathway in the pathogenesis of inflammatory bowel disease, it is not possible to rule out the potential for an increased risk of aggravation or precipitation of Crohn's disease.

Overall, the benefit-risk balance of SEK for the proposed indication of use in adult patients with moderate to severe PsA is favourable. The recommended dose for most patients is 150 mg given by SC injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. The sponsor has requested a dose modification be approved in patients who are anti TNF-IR or with concomitant moderate to severe PSOR. The recommended dose of SEK in those 2 subgroups is 300 mg by SC injection with initial dosing at weeks 0, 1, 2 and 3 followed by monthly 300 mg injections starting at week 4. The current dataset shows a favourable benefit-risk assessment with the proposed posology. In addition, the use of SEK with or without concurrent MTX has been adequately justified in this submission.

9.3.2. Ankylosing spondylitis

The overall benefit-risk balance of SEK in adult patients with moderately- severely active AS is favourable. AS is a chronic inflammatory arthritis that predominately affects the spine and can result in significant functional loss and disability. The main treatment options available at present are NSAID drugs and physiotherapy. There is limited or no supporting evidence for the use of conventional DMARD drugs such as MTX. Although there are 5 anti TNF drugs approved in Australia for the treatment of active AS, a significant proportion of patients do not achieve optimal or adequate clinically meaningful response. Other limitations to currently available therapies in Australia include slow onset of action, diminished efficacy over time and drug specific safety concerns such as opportunistic infection (including TB), malignancy (for example, lymphoma) and various laboratory test abnormalities (for example, abnormal liver function tests and cytopenia). Thus, there remains a significant unmet need for new drugs with unique mechanisms that can provide a rapid onset of effect, improved and sustained symptom improvement and a safety profile that allows for long term use.

SEK is a fully human IgG1 monoclonal antibody that selectively binds to and neutralizes the pro-inflammatory cytokine, IL-17A. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of AS. In this submission, SEK has been evaluated in a large clinical program which complied with CHMP guidelines for evaluation of treatments in AS. The clinical studies evaluated an adequate number of subjects in the target patient population and demonstrated that SEK is an efficacious treatment in active AS. The minimum most effective dose of SEK demonstrated in the Phase III study program was 150 mg injections. The superior efficacy of SEK versus PBO was consistent in most subgroups, such as age, gender, race and concomitant therapies. However, subjects with a baseline body weight >90 kg and/or a history of anti TNF-IR had a lower clinical response to SEK compared to other patient subgroups, but still a better response to SEK than PBO.

The risk profile of SEK is based on a total of 571 SEK treated patients with AS involved in the 2 pivotal Phase III studies as well as additional safety information collected from >4000 patients treated with any dose of SEK across a variety of autoimmune diseases. In the AS clinical program, there was no evidence of an imbalance of SAEs with SEK compared to PBO. There was an increased incidence in overall infections in the SEK dose groups compared to PBO, which was not dose dependent. The majority of reported infections were mild or moderate, upper respiratory tract infections. Candida infections were also more frequent with SEK (irrespective of dose) compared to PBO. Most Candida infections were localised mucosal events, consistent with the drug mechanism of action. There was also an increased frequency of herpes infection (mainly, oral or genital) with SEK treatment. A few serious opportunistic infections, such as disseminated cutaneous herpes zoster, were reported with SEK. However, this is included in the proposed PI. No tuberculosis or viral hepatitis reactivation was observed in any AS trial.

Neutropenia was more frequently observed with SEK than placebo, but most cases were of mild severity (CTCAE grade 1-2), transient and reversible. More severe neutropenia (CTCAE grade 3) was also infrequently observed with SEK, but was not associated with an increase in infection. There was a small increase in incidence of mild hepatic transaminase elevations and dyslipidaemia with SEK versus PBO, which was not dose related.

Malignancy represents a theoretical risk with any immunosuppressive therapy, but there is no evidence that SEK confers an increased risk for malignancy in the current dataset of medium drug exposure. Due to the potential involvement of the IL-17 pathway in the pathogenesis of inflammatory bowel disease, it is not possible to rule out the potential for an increased risk of aggravation or precipitation of Crohn's disease.

Overall, the benefit-risk balance of SEK for the proposed indication of use in adult patients with moderate to severe AS is favourable. The recommended dose in adult patients with active AS is 150 mg given by SC injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4.

10. First round recommendation regarding authorisation

10.1. Psoriatic arthritis

The evaluator recommends acceptance of the sponsor's proposed extension of treatment indication for SEK to include the treatment of adult patients with active PsA. The current submission provides robust evidence of improving the symptoms and signs of active PsA, as well as improving physical functioning and health related QOL. The proposed wording of treatment extension in patients with PsA has an additional element relating to its use as monotherapy or in combination with MTX. The current dataset supports the claim that the concurrent use of MTX does not significantly impact upon either efficacy or safety in the adult PsA population. The sponsor has also requested for PsA patients who are anti TNF-IR or patients with concomitant moderate to severe PSOR, the recommended dose of SEK is 300 mg by SC injection with initial dosing at weeks 0, 1, 2 and 3 followed by monthly 300 mg injections starting at week 4. There is a sufficient volume of data to indicate that the higher dose of SEK (300 mg versus 150 mg injections) is the most efficacious dose in this subset of patients, with a relatively low increased risk of safety concerns. Initially, the sponsor had proposed additional wording for the treatment extension in patients with PsA to include a claim of inhibition of structural progression of peripheral joint damage by X-ray. This has subsequently been withdrawn from the sponsor at this stage, which is appropriate. Although there is preliminary evidence of a radiographic benefit with SEK, this has not been sufficiently proven at this stage, and requires further evidence of justification before registration is approved. In particular, the current X-ray data is limited to 52 weeks of assessment which is an insufficient time frame to evaluate such a claim. It would be important to review the 2 year radiographic data from the pivotal Phase III Study to determine if a robust treatment effect with SEK could be observed.

Should approval of the sponsor's proposed extension of indication be granted, the evaluator also recommends that approval of the sponsor's proposed extension of indication be subject to:

- Satisfactory response to the questions in this report,
- Regular periodic safety update reports, and
- When available, the sponsor provides TGA with the final clinical study reports for Studies F2306 and F2312.

10.2. Ankylosing spondylitis

The evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for SEK to include the treatment of adult patients with active AS. The current submission provides robust evidence of improving the symptoms and signs of active AS, as well as improving physical functioning and health related QOL. The sponsor has asked for approval of a single dose strategy in this treatment indication being SEK is 150 mg given by SC injection

with initial dosing at weeks 0, 1, 2 and 3 (loading regimen) followed by monthly injection starting at week 4 (maintenance treatment phase). This dosing posology has been demonstrated to be the minimum most effective approach with a comparable safety to the lower dose of SEK (75 mg injections) examined in the AS clinical development program.

The evaluator would also recommend that approval of the sponsor's proposed extension of indication be subject to:

- Satisfactory response to the questions in this report,
- Regular periodic safety update reports, and
- When available, the sponsor provides TGA with the final clinical study reports for Studies F2305 and F2310.

11. Clinical questions

11.1. Pharmacokinetics

Nil

11.2. Pharmacodynamics

Nil

11.3. Efficacy

11.3.1. Psoriatic arthritis

1. In the FUTURE-1 trial it was reported that approximately 25% of all enrolled subjects had recorded protocol deviations by week 24, and in the FUTURE-2 study it was reported that approximately 15% of all enrolled subjects had recorded protocol deviations up to week 24. Could the sponsor provide further specific detail on the nature of the protocol deviations beyond the reported categories of "GCP related deviations" and "key procedures not performed as per protocol", and outline if and how such deviations may have potentially impacted upon the efficacy results.

2. In both Phase III studies in PsA (FUTURE-1 and FUTURE-2), no sensitivity analysis of the primary and secondary efficacy endpoints using the per-protocol populations were provided. Could the sponsor state the reason for this approach and whether or not the primary efficacy hypothesis was still achieved if the per protocol population was investigated in the analysis.

3. In both Phase III PsA (FUTURE-1 and FUTURE-2) studies, the mean change from baseline to week 24 in the SF-36 PCS scores was a pre-specified secondary endpoint. Could the sponsor provide the baseline SF-36 PCS scores for each treatment group in both trials, so the absolute change from baseline can be considered?

4. Can the sponsor provide an analysis of the X-ray data (vdH-mTTS) in the FUTURE-1 study by subject weight (≤100 kg versus >100 kg)? In the PSUMMIT studies investigating the effectiveness of ustekinumab in PsA, subjects weighing >100 kg were observed to have no treatment related benefit in terms of X-ray progression. Was the same observation seen with SEK?

5. For subjects weighing ≥100 kg in the FUTURE-2 trial, only those treated with SEK 300 mg injections (and not the proposed alternative 150 mg dose) were observed to have a statistically

higher rate of ACR20 response at 24 weeks compared with placebo. Could the sponsor comment on whether the 300 mg dose posology should be recommended in subjects weighing ≥100 kg?

11.3.2. Ankylosing spondylitis

6. In both pivotal Phase III studies in AS (MEASURE-1 and MEASURE-2), the rate of ASAS20 response at week 16 (primary efficacy endpoint) was numerically lower in subjects weighing >90 kg (versus subjects weighing <90 kg) who received the proposed registration dose of SEK (150 mg injections) for this treatment indication. Could the sponsor comment on the clinical relevance of this observation and whether or not a higher dose of SEK (for example, 300 mg injections) should be investigated in this patient subgroup.

11.3.3. Both treatment indications

7. Presumably, there are differences in the viscosity of SEK and placebo injections for subcutaneous administration. Could the sponsor outline what specific procedures may have been used in the pivotal Phase III PsA and AS studies to overcome this potential bias related to the blinding of SC administered study treatment?

11.4. Safety

Nil

12. Second round evaluation of clinical data

The sponsor's Section 31 response dated December 14, 2015 addresses 7 questions that were raised in the first round clinical assessment.

- *Q1. In the FUTURE-1 trial it was reported that approximately 25% of all enrolled subjects had recorded protocol deviations by week 24, and in the FUTURE-2 study it was reported that approximately 15% of all enrolled subjects had recorded protocol deviations up to week 24. Could the sponsor provide further specific detail on the nature of the protocol deviations beyond the reported categories of "GCP related deviations" and "key procedures not performed as per protocol", and outline if and how such deviations may have potentially impacted upon the efficacy results.*

In the S31 response, the sponsor has provided detailed additional information on the nature of the protocol deviations in both the FUTURE-1 and FUTURE-2 studies. Up to week 24 in the FUTURE-1 trial (Study F2306), a total of 166 subjects (27.4% of 606) had documented protocol deviations and these occurred at a similar incidence in each of the 3 treatment groups: 28.7% (58/202) in the SEK 75 mg group, 23.8% (48/202) in the SEK 150 mg arm and 29.7% (60/202) in the PBO group. The 2 most common reasons for protocol deviations in this study were "key procedures not performed as per protocol" (12.9% [26/202] in the SEK 75 mg group, 8.9% [18/202] in the SEK 150 mg arm and 6.9% [14/202] in the PBO group) and "GCP related deviations" (12.4% [25/202] in the SEK 75 mg group, 6.4% [13/202] in the SEK 150 mg arm and 9.4% [19/202] in the PBO group). In the S31 response, the sponsor has provided additional information about these 2 categories of protocol deviations. In the category of "key procedures not performed as per protocol", the 3 most common types of deviations were: joint count assessments not performed by the independent joint assessor (i.e. assessments were made by the principal or co-investigator) which affected 5 patients in the SEK 75 mg group, 8 patients in the SEK 150 mg arm and 6 patients in the PBO group; study treatment administered to patient by unblinded personnel (5 patients in the SEK 75 mg group, 4 patients in the SEK 150 mg arm and 7 patients in the PBO group), and X-ray not performed at appropriate visit (10 patients in the SEK 75 mg group, 1 patient in the SEK 150 mg arm and 3 patients in the PBO group). In the category of "GCP-related deviation", the 3 most common types of deviations were: non-

compliance with investigator responsibilities (affecting 13 patients in the SEK 75 mg group, 8 patients in the SEK 150 mg arm and 10 patients in the PBO group); incorrect or missing responder status recorded in the interactive response technology (10 patients in the SEK 75 mg group, 2 patients in the SEK 150 mg arm and 6 patients in the PBO group); and pharmacogenomic blood sample collected without signed consent (2 patients in the SEK 75 mg group, 3 patients in the SEK 150 mg arm and 1 patient in the PBO group).

Up to week 24 in the FUTURE-2 trial (Study 2312), a total of 64 subjects (16.0% of 397) had documented protocol deviations and these were recorded at a lower rate in the SEK 75 mg group (13.1%; 13/99), but at a higher and similar incidence in each of other 3 treatment groups (15.0% [15/100] in the SEK 75 mg group, 18.0% [18/100] in the SEK 150 mg arm and 18.4% [18/98] in the PBO group). The most common reason for a protocol deviation in this study was "GCP related deviation", which affected 6.1% (6/99) in the SEK 75 mg group, 3.0% (3/100) in the SEK 150 mg arm, 4.0% (4/100) in the SEK 300 mg group and 8.2% (8/98) in the PBO arm. The most common types of deviations in this category were: incorrect or missing response assessment at week 16 to enable re-assignment (3 patients each in the SEK 75 mg and 300 mg groups, 4 subjects in the PBO arm and 1 patient in the SEK 150 mg group); non-compliance with investigator responsibilities (4 patients in the PBO group, 2 subjects each in the SEK 75 mg and 150 mg arms and no patients in the SEK 300 mg group); and pharmacogenomic blood sample collected without signed consent (1 patient each in the SEK 75 mg, SEK 300 mg and PBO groups).

In conclusion, the sponsor has provided a detailed explanation of the recorded protocol deviations up to week 24 in both of the pivotal studies (FUTURE-1 and FUTURE-2) supporting the claim of treatment benefit with SEK in patients with active PsA. In the response to Q2 (below), the sponsor has provided a sensitivity analysis after the exclusion of protocol deviators from the analysis set. The protocol deviations in both Phase 3 PsA trials have not impacted the efficacy results and do not change the initial overall interpretation of the data in favour of SEK treatment versus PBO.

- *Q2. In both Phase 3 studies in psoriatic arthritis (FUTURE-1 and FUTURE-2), no sensitivity analysis of the primary and secondary efficacy endpoints using the per-protocol populations were provided. Could the sponsor state the reason for this approach and whether or not the primary efficacy hypothesis was still achieved if the per protocol population was investigated in the analysis.*

In the S31 response, the sponsor has provided an analysis of the primary efficacy endpoint (ACR20 response rate) and the key secondary clinical efficacy endpoint (ACR50 response rate) at 24 weeks in both Phase 3 PsA studies using the per-protocol population. This dataset used NRI and was analysed using a logistic regression model.

In the FUTURE-1 study, both doses of SEK (75 mg and 150 mg) were statistically superior to PBO for the rate of ACR20 and ACR50 response at 24 weeks ($p<0.0001$) using the per-protocol subgroup of the FAS. At week 24, the ACR20 response rate was 53.0% (80/151) for SEK 75 mg therapy, 50.9% (84/165) for SEK 150 mg treatment and 15.4% (24/156) for PBO. This data is highly similar to that observed in the original FAS with no subject exclusions, whereby the ACR20 response rate at 24 weeks was 50.5% (102/202) for SEK 75 mg, 50.0% (101/202) for SEK 150 mg and 17.3% (35/202) for PBO. At week 24 in the FUTURE-1 Study, the ACR50 response rate was 32.5% (49/151) for SEK 75 mg, 36.4% (60/165) for SEK 150 mg and 6.4% (10/156) for PBO. Again, this was highly similar to the data seen in the original FAS without patient exclusions, where the rate of ACR50 response was 30.7% (62/202) for SEK 75 mg, 34.7% (70/202) for SEK 150 mg and 7.4% (15/202) for PBO therapy.

In the FUTURE-2 study, the 2 higher doses of SEK (150 mg and 300 mg) were statistically superior to PBO for the rate of ACR20 and ACR50 response at 24 weeks ($p<0.0001$) using the per-protocol subgroup of the FAS. Consistent with the primary analysis, the SEK 75 mg dose

arm showed numerically higher response rates (for both ACR20 and ACR50), which was not statistically superior to PBO. At week 24, the ACR20 response rate in the per-protocol population was 31.1% (28/90) for SEK 75 mg therapy, 50.0% (46/92) for SEK 150 mg treatment, 56.7% (51/90) for SEK 300 mg and 14.3% (12/84) for PBO. This data is highly similar to that observed in the original FAS with no subject exclusions, whereby the ACR20 response rate at 24 weeks was 29.3% (29/99) for SEK 75 mg, 51.0% (51/100) for SEK 150 mg, 54.0% (54/100) for SEK 300 mg and 15.3% (15/98) for PBO. At week 24 in the FUTURE-2 Study, the ACR50 response rate was 18.9% (17/90) for SEK 75 mg, 35.9% (33/92) for SEK 150 mg, 36.7% (33/90) for SEK 300 mg and 7.1% (6/84) for PBO. Again, this was highly similar to the data seen in the original FAS without patient exclusions, where the rate of ACR50 response was 18.2% (18/99) for SEK 75 mg, 35.0% (35/100) for both SEK 150 mg and 300 mg, and 7.1% (7/98) for PBO therapy.

In conclusion, the analysis of the 2 key clinical efficacy endpoints (ACR20 and ACR50 response rate at 24 weeks) using the per-protocol dataset was consistent with the observed results in the FAS cohort without subject exclusions (primary analysis). The exclusion of protocol violators from the efficacy analysis supports the evidence of beneficial effect with SEK seen in the primary analysis as being scientifically robust.

- *Q3. In both Phase 3 psoriatic arthritis (FUTURE-1 and FUTURE-2) studies, the mean change from baseline to week 24 in the SF-36 PCS scores was a pre-specified secondary endpoint. Could the sponsor provide the baseline SF-36 PCS scores for each treatment group in both trials, so the absolute change from baseline can be considered?*

In the S31 response, the sponsor has provided a Table (2.9) which summarises the baseline SF-36 PCS scores as well as the absolute score and change from baseline to week 24 (using observed data) in both the FUTURE-1 and FUTURE-2 studies. An improvement from baseline of >2.5 points in the PCS is defined as a clinically meaningful improvement in patients with active PsA.

At baseline in Study F2306 (FUTURE-1), the mean baseline SF-36 PCS scores were highly similar between the 3 treatment groups ranging from 36.16 to 36.90. At 24 weeks, numerically greater improvements in the mean change from baseline in the SF36-PCS score were reported for both doses of SEK (5.89 for the 75 mg dose group [n=191] and 6.65 for the 150 mg arm [n=190]) compared to PBO (3.77; n=182).

At baseline in Study F2312 (FUTURE-2), the mean baseline SF-36 PCS scores were similar between the 4 treatment groups ranging from 36.15 to 37.44 (slightly higher in the PBO group). At 24 weeks, numerically greater improvements in the mean change from baseline in the SF36-PCS score were reported for all 3 doses of SEK with an apparent dose response relationship (4.70 for the 75 mg dose group [n=91], 6.60 for the 150 mg arm [n=96] and 7.48 for the 300 mg group [n=96] compared to PBO (3.75; n=88).

In summary, the mean change from baseline to week 24 for the SF-36 PCS in both Phase 3 PsA studies was numerically higher with all examined doses of SEK versus PBO, but a moderately beneficial PBO response rate was also observed in both trials. Nonetheless, the pre-specified statistical endpoint of the LS mean change from baseline to week 24 in the SF-36 PCS was statistically in favour of a treatment response with all doses of SEK versus PBO.

- *Q4. Can the sponsor provide an analysis of the X-ray data (vdH-mTTS) in the FUTURE-1 study by subject weight (≤100 kg versus >100 kg)? In the PSUMMIT studies investigating the effectiveness of ustekinumab in psoriatic arthritis, subjects weighing >100 kg were observed to have no treatment related benefit in terms of X-ray progression. Was the same observation seen with secukinumab?*

In the S31 response, the sponsor has proposed an alternative subject weight cut-off value of 90 kg (versus 100 kg) based on the available number of subjects in each subgroup. This is an

acceptable proposal for analysis of this question. A total of 202 subjects were included in each of the 3 treatment groups in Study F2306 (FUTURE-1). Using a cut-off subject weight of ≥90 kg, a total of 57 patients were included in each SEK treatment group and 49 subjects in the PBO arm met the cut-off value. If a cut-off subject weight of ≥100 kg was alternatively used, a total of 39-41 patients in each SEK treatment group and 30 subjects in the PBO arm met the cut-off value.

Using the FAS cohort of subjects weighing <90 kg and with linear extrapolation of missing data, the mean change from baseline to week 24 in the total vdH-mTSS was -0.03 in the SEK 75 mg group (n=124; mean baseline score of 22.81) and -0.02 in the SEK 150 mg arm (n=128; mean baseline score of 25.18). For subjects weighing ≥90 kg, the mean change from baseline to week 24 in the total vdH-mTSS increased somewhat (i.e. worsened) in both SEK treatment groups: 0.13 in the SEK 75 mg group (n=57; mean baseline score of 13.93) and 0.49 in the SEK 150 mg arm (n=57; mean baseline score of 14.98). The sponsor has not presented a formal statistical analysis of the treatment related comparison according to subject weight, but the absolute results are suggestive of a diminished radiographic benefit with SEK (either dose) in patients with a body weight ≥90 kg versus those with a body weight <90 kg. The sponsor asserts that the magnitude of change from baseline to week 24 in the mean vdH-mTSS (using the FAS cohort and linear extrapolation) is below the level of minimally clinically important difference, and that SEK treatment minimises structural progression in patients irrespective of weight (<90 versus ≥90 kg). There is no established level of minimal clinically important difference in mean change from baseline in the total vdH-mTSS for patients with PsA, although often data is presented by the proportion of subjects according to the arbitrary cut-off change of ≤0.5 points over 24-52 weeks. The sponsor has not presented the subject weight strata X-ray data in this format in the S31 response. Although no formal statistical analysis has been presented in the S31 response, I do not agree with the sponsor statement. Furthermore, the extended radiographic follow-up data (i.e. collected at week 52) shows a greater (and progressive) increase from baseline in the mean total vdH-mTSS in patients of higher subject weight.

At 52 weeks using the FAS cohort of subjects weighing <90 kg and linear extrapolation of missing data, SEK 75 mg injections resulted in a mean change from baseline in the total vdH-mTSS of 0.14 (n=127) and SEK 150 mg therapy produced a mean change from baseline of 0.27 (n=129). For both SEK doses, the mean change from baseline to week 52 in the total vdH-mTSS was greater in magnitude for subjects weighing ≥90 kg. For subjects weighing ≥90 kg, SEK 75 mg therapy resulted in a mean change from baseline in the total vdH-mTSS of 0.39 (n=60) and SEK 150 mg treatment produced a mean change from baseline of 0.59 (n=60).

Like the primary data, the mean increases in total vdH-mTSS (both at 24 and 52 weeks) were predominately explained by increases in ES for all patient groups. The 2 year radiographic data for the patients who received SEK from the outset in this trial will be important to assess for determining maintenance of minimising structural progression with continued SEK therapy, particularly in those subjects of higher weight.

In summary, the radiographic data at weeks 24 and 52 suggest that patients with a higher subject weight (≥90 kg) have larger absolute mean increases (i.e. more X-ray progression) from baseline in the total vdH-mTSS than subjects weighing <90 kg, regardless of SEK dose. The observation of reduced radiographic benefit with SEK in patients of increased weight is consistent with that seen with other biological therapies (e.g. ustekinumab and anti-TNF drugs) in PsA.

- *Q5. For subjects weighing ≥100 kg in the FUTURE-2 trial, only those treated with secukinumab 300 mg injections (and not the proposed alternative 150 mg dose) were observed to have a statistically higher rate of ACR20 response at 24 weeks compared with placebo. Could the sponsor comment on whether the 300 mg dose posology should be recommended in subjects weighing ≥100 kg.*

In the S31 response, the sponsor asserts that an analysis of the weight-efficacy relationship over time by weight groups of <100 kg versus ≥100 kg in the FUTURE-2 study, and by weight groups of <90 kg versus ≥90 kg in the 2 pivotal Phase 3 PsA trials does not provide sufficient evidence to suggest a weight-based posology for SEK in adults with active PsA. In the FUTURE-2 Study, the rate of ACR20 response at 24 weeks for patients weighing <100 kg was similar for the SEK 150 mg (65.7%; 44/67) and 300 mg dose groups (67.1%; 55/82), both of which were greater than that observed in the SEK 75 mg dose arm (54.1%). For the subgroup of patients weighing ≥100 kg, the difference in the ACR20 response rate was similar between the subject weight subgroups (<100 kg versus ≥100 kg) in the SEK 300 mg dose group (67.1% [55/82] for <100 kg and 61.1% [11/18] for ≥100 kg). However, the 24-week rate of ACR20 response decreased by 20% with increasing subject weight in the SEK 150 mg dose group (65.7% [44/67] for <100 kg versus 45.5% [15/33] for ≥100 kg). The sponsor states that although there appears to be a modest treatment difference in ACR20 response in patients weighing ≥100 kg who received SEK 150 mg injections, the result interpretation is limited by the low number of evaluable patients in the ≥100 kg analysis. Although randomisation was not stratified by body weight in the FUTURE-2 Study, ACR20 responses at 24 weeks in the subgroup of patients weighing ≥100 kg, was only statistically higher with SEK 300 mg therapy (61.1%; 11/18) compared to PBO (10.0% [2/20]; p=0.0029). Treatment with SEK 75 mg (28.0%; 7/25) or SEK 150 mg injections (45.5%; 15/33) was not statistically better than PBO in the patient cohort weighing ≥100 kg (p=0.1725 and p=0.0795, respectively).

In the FUTURE-2 Study, an analysis of a treatment-by-subject weight interaction was also performed for the higher levels of clinical response (i.e. ACR50 and ACR70 response rates at 24 weeks). For the subgroup of patients weighing <100 kg, the ACR50 response rate at week 24 was similar (<5% difference in response rate) for the SEK 150 mg (41.8%; 28/67) and 300 mg dose groups (37.8%; 31/82). For subjects weighing ≥100 kg, the ACR50 response rates were somewhat higher (8.6% difference in response rate) in the 300 mg (38.9%; 7/18) versus the 150 mg dose arm (30.3%; 10/33). For patients weighing <100 kg, the rate of ACR70 response at week 24 was similar for the 150 mg and 300 mg dose groups (23.9% [16/67] and 24.4% [20/82], respectively). For the subjects weighing ≥100 kg, the ACR70 response rates were also similar in the 150 mg and the 300 mg dose groups (15.2% [5/33] and 11.1% [2/18], respectively). Overall, the rates of ACR20 and ACR50 response at 24 weeks appear to indicate a clinically relevant difference in clinical response with SEK 300 mg versus 150 mg therapy in subjects weighing >100 kg, but this was not seen at the highest level of clinical response (ACR70 response). The limitations of this subgroup analysis include overall small patient numbers in each examined subgroup and therefore a lack of statistical power to determine a statistically significant difference in clinical response. The data suggests a dose response relationship with SEK with respect to subject weight and this is supported by the population PK results outlined elsewhere in this report. In the population PK model, subject weight was identified as a significant covariate factor influencing the clearance and apparent volume of distribution of SEK. Lower SEK C_{min} values at steady state are likely in to occur in heavier patients and there is a trend to higher rates of clinical response in patients with higher C_{min} concentrations (>20 µg/mL).

In the S31 response, the sponsor has also provided an analysis of ACR response rates at 24 weeks in the FUTURE-2 Study by a alternative subject weight cut-off value (<90 kg versus ≥90 kg), and by prior anti-TNF exposure status (naïve versus experienced). Based on the totality of the dataset, there does not appear to be a dose-response relationship with respect to subject weight (<90 kg versus ≥90 kg) with SEK in anti-TNF naïve patients. For anti-TNF experienced subjects (regardless of subject weight), there are higher observed ACR response rates with SEK 300 mg therapy versus 150 mg injections, but this variation to posology (based on prior anti-TNF exposure) is already part of the sponsor proposal in this submission for treating patients with active PsA.

The sponsor has also simulated SEK concentrations with the exposure-response relationship using data from the FUTURE-2 Study. The model estimates that the median difference in the ACR20 response rate is expected to be 9.2% for SEK 300 mg versus 150 mg dose in patients weighing ≥90 kg, but with significant imprecision in the estimated exposure-response relationship (95% CI: 1.5% –17.3%). A difference in the rate of ACR20 treatment response of almost 10% would be clinically meaningful. However, the supporting clinical endpoints (ACR50 and ACR70 response, DAS28-CRP remission and HAQ-DI responder status) show a much lower dose related difference (between 4.2% and 6.7% difference) for SEK 300 mg versus 150 mg therapy in patients weighing ≥90 kg.

In conclusion, clinical data and simulated modelling does not provide evidence to support a weight-based posology for SEK in anti-TNF experienced adult patients with active PsA, but there is some data to suggest that anti-TNF naïve patients weighing >100 kg may require higher doses of SEK (300 mg injections) to achieve satisfactory clinical response (e.g. ACR20 and ACR50 response). However, this dataset has several limitations (including small patient numbers) and is not consistently in favour of adopting a weight-based posology for SEK in heavier subjects who are anti-TNF naive. There is a relatively high prevalence of obesity in adult patients with PsA so the issue of SEK dosing in subjects of higher body weight is an issue of significant clinical relevance.

- *Q6. In both pivotal Phase 3 studies in ankylosing spondylitis (MEASURE-1 and MEASURE-2), the rate of ASAS20 response at week 16 (primary efficacy endpoint) was numerically lower in subjects weighing >90 kg (versus subjects weighing <90 kg) who received the proposed registration dose of secukinumab (150 mg injections) for this treatment indication. Could the sponsor comment on the clinical relevance of this observation and whether or not a higher dose of secukinumab (e.g. 300 mg injections) should be investigated in this patient subgroup.*

In the S31 response, the sponsor asserts that an analysis of the weight-efficacy relationship over time by weight groups of <90 kg versus >90 kg in the 2 pivotal Phase 3 AS studies does not provide sufficient evidence to suggest a weight-based posology for SEK in adults with active AS. The PBO-adjusted treatment effect for the rate ASAS20 response at 16 weeks for the 150 mg SEK dose in patients weighing >90 kg was 22-30% (pooled group data from the 2 pivotal studies), the PBO-treatment difference had a very wide 95% CI that crossed zero (-1 to +61%). Furthermore, simulation data from the MEASURE-2 Study, indicates that higher levels of clinical response (e.g. ASAS40 response and ASAS partial remission) reveal smaller differences in treatment difference (<5% difference) when SEK 300 mg versus 150 mg dose is used in adult patients with active AS.

In conclusion, clinical data and simulated modelling does not provide sufficient evidence to support a weight-based posology for SEK in adult patients with active AS, but there is some preliminary data (based on very small patient numbers) to suggest that patients weighing >90 kg may require higher doses of SEK (300 mg injections) to achieve satisfactory clinical response (e.g. ASAS20 response). Fortunately, there is a relatively low prevalence of obesity in adult patients with AS so the issue of SEK dosing in subjects of higher body weight is not a common issue of significant clinical relevance.

- *Q7. Presumably, there are differences in the viscosity of secukinumab and placebo injections for subcutaneous administration. Could the sponsor outline what specific procedures may have been used in the pivotal Phase 3 psoriatic arthritis and ankylosing spondylitis studies to overcome this potential bias related to the blinding of subcutaneously administered study treatment.*

The sponsor states that all SEK and PBO solutions used in all Phase 3 studies of the clinical development program were “almost colourless” and “practically free of visible particles”. In addition, the sponsor did not receive any qualitative feedback from site investigators or subjects of a distinguishable physical appearance between any of the study treatments. The sponsor

comments that injection resistance (at the skin and SC tissue) would also be similar. The different study formulations had minor differences in osmolality, which are of no clinical relevance. Overall, the sponsor has adequately explained that potential unintentional unblinding of study treatment (SEK and PBO solutions) due to differences in physical appearance would seem of very low likelihood.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of SEK for the treatment of adult patients with active PsA or AS in the proposed usage are unchanged from those identified in this report. In particular, the Phase III PsA studies (FUTURE-1 and FUTURE-2) are well conducted trials, which demonstrate a robust and clinically meaningful efficacy benefit with SEK versus PBO. Furthermore, the proposed dosing regimens in each treatment indication have been reasonably justified, particularly in the patient circumstance of high body weight (≥90 kg).

13.2. Second round assessment of risks

No new clinical safety information was requested of or submitted by the sponsor in response to questions from the first round clinical evaluation. Accordingly, the risks of SEK are unchanged from those identified in this report.

13.3. Second round assessment of benefit-risk balance

13.3.1. Psoriatic Arthritis

After consideration of the responses to the clinical questions, there is no change to the opinion expressed. The benefit-risk balance of SEK injections in the proposed treatment indication of active PsA in adult patients is favourable. Clinically relevant, robust efficacy has been observed with SEK in the treatment of PsA, particularly in the Phase III studies where the majority of subjects (70-83%) had prior exposure to conventional DMARD therapy. Unfavourable effects consistent with other biologic therapies have been observed with SEK, including infections and cases of mild neutropenia. Although a higher incidence of localised mucosal Candida and herpes virus infections were observed with SEK, there was no increased prevalence of mycobacterial or serious opportunistic infections.

13.3.2. Ankylosing spondylitis

After consideration of the responses to the clinical questions, there is no change to the opinion expressed. The benefit-risk balance of SEK injections in the proposed treatment indication of active AS in adult patients is favourable. Clinically relevant efficacy has been observed with SEK in the treatment of AS, and the nature and risk of side effects with SEK is consistent with other biologic therapies used in adult patients with active AS.

14. Second round recommendation regarding authorisation

14.1. Psoriatic arthritis

The evaluator recommends acceptance of the sponsor's proposal for an extension of treatment indication for SEK to include active PsA. Based on the data available, SEK alone or in combination with MTX is effective and demonstrates a comparable and an acceptable safety profile to other biologic therapies in the management of active PsA in adult patients, particularly in those who have failed to respond to prior conventional DMARD and/or anti TNF treatment. Furthermore, on the balance of scientific evidence, the sponsor proposed posology for SEK is sufficiently acceptable based on the current available data.

Should approval of the sponsor's proposed extension of indication be granted, the evaluator also recommends that approval of the sponsor's proposed extension of indication be subject to:

- Regular periodic safety update reports, and
- When available, the sponsor provides TGA with the final clinical study reports for Studies F2306 and F2312.

14.2. Ankylosing spondylitis

The evaluator recommends acceptance of the sponsor's proposal for an extension of treatment indication for SEK to include active AS. Based on the data available, SEK is effective and demonstrates a comparable and an acceptable safety profile to other biologic therapies in the management of active AS in adult patients, including those who may have failed to respond to anti TNF treatment. Furthermore, the sponsor proposed posology for SEK is acceptable based on the current available dataset.

The evaluator would also recommend that approval of the sponsor's proposed extension of indication be subject to:

- Regular periodic safety update reports, and
- When available, the sponsor provides TGA with the final clinical study reports for Studies F2305 and F2310.

15. References

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15.2. Ankylosing spondylitis

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