Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Linagliptin

Proprietary Product Name: Trajenta

Sponsor: Boehringer Ingelheim Pty Ltd

November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

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 <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ACPM	Australian Committee for Prescription Medicines
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
AUCG	area under glucose curve
BI	Boehringer Ingelheim
BMI	body mass index
CEC	clinical event committee
CER	clinical evaluation report
CI	confidence interval
CMI	consumer medicine information
CTD	common technical document
DPP-4	dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDC	fixed dosage combination
FPG	fasting plasma glucose
GIP	glucose-dependent inhibitory peptide
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1C
IVRS	interactive voice response system
LOCF	last observation carried forward
MACE	major adverse cardiovascular event

Abbreviation	Meaning
MDRD	modification of diet in renal disease
NPH	Neutral Protamine Hagedorn
OHA	oral hypoglycaemic agent
PCSA	possibly clinically significant laboratory abnormality
PI	product information
PK	pharmacokinetic
PPS	per protocol set
PV	protocol violation
RMP	risk management plan
SAE	serious adverse event
SCS	Summary of Clinical Safety
SD	standard deviation
SI	Systeme Internationale
SOC	system organ class
SU	sulphonylurea
SWS	switched set
TGA	Therapeutic Goods Administration
TZD	thiazolidinedione
T2DM	type 2 diabetes mellitus

1. Clinical rationale

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder principally characterised by hyperglycaemia. Its incidence and prevalence is increasing in developed countries, associated with a parallel increase in obesity contributed to by excessive and qualitatively inappropriate food intake and reduced physical activity. The pathogenesis of T2DM includes insulin resistance together with a relative impairment of insulin secretion which tends to progress over time. Part of the insulin deficiency is represented by a diminution in the "incretin effect", the physiological mechanism by which post-prandial insulin secretion is enhanced as a result of insulin secretagogues (incretins) being released into the circulation from the upper gastrointestinal tract following feeding. Linagliptin is an inhibitor of DPP-4, the enzymatic activity of which

includes as substrates the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent inhibitory peptide (GIP). Levels of these incretins are therefore increased following administration of linagliptin, which thus lowers blood glucose by enhancing insulin response to feeding.

This action of linagliptin and other DPP-4 inhibitors in improving post-prandial insulin secretion is different from and is complementary to the actions of other oral hypoglycaemic agents (OHA) currently in use and mentioned in the current and proposed indications for Trajenta. Metformin improves glucose disposal by mechanisms which are not entirely clear but which are not dependent on insulin, and can be regarded as improving insulin sensitivity. Sulphonylureas (SU) stimulate insulin secretion more directly and can do so in the fasting state or at normal blood glucose levels, hence being more prone than other OHA to cause hypoglycaemia. Thiazolidinediones (TZD) counter insulin resistance by improving response to insulin at the post-receptor level. Combinations of these classes of OHA, including DPP-4 inhibitors such as linagliptin, are therefore rational as their various actions are all directed at improving the quantum of insulin action on its target metabolic pathways; as is the supplementary administration of insulin itself, hence combination of any OHA class with insulin also is a hypothetically rational basis for therapy.

Appropriate medical management of T2DM is guided by clinical algorithms such as that contained within the consensus statement of the American Diabetes Association and European Association for the Study of Diabetes.[1] This, like other similar guidelines, gives primacy to the introduction of lifestyle measures and to metformin as the drug of first choice for pharmacotherapy. The role of the other drug classes mentioned above, and the hierarchy which might govern their order of introduction into T2DM Management, is less clearly defined. Metformin (except in the United States) and SU have both been in use for over 50 years, whereas TZD and incretin based therapies, including GLP-1 analogues as well as DPP-4 inhibitors, have been introduced much more recently and best practice with regard to their appropriate use remains in a state of evolution. To further compound the situation, there remains some use of other OHA classes introduced earlier such as glinides (such as repaglinide) and alpha glucosidase inhibitors such as acarbose which is registered in Australia and voglibose which is not but which is used in one of the studies in the submission. Additionally, the recognition that the pathogenesis of T2DM includes a variable but significant element of insulin deficiency has led to an increasing use of insulin in the management algorithm. This in turn has led to the need for studies, such as some of those included in this submission, which examine the efficacy and safety of OHA used in conjunction with insulin therapy.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission was well presented and indexed and easy to navigate in electronic format. In order to address the rather complex overlap between the datasets supporting this application and the three related submissions, a detailed tabular listing of the clinical studies submitted in support of all four applications was provided by the sponsor. The sponsor has provided annotations indicating which studies have already been evaluated by the TGA in the related submissions.

[1] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman R, Sherwin R, Zinman B. (2009). Medical management of hyperglycaemia in type II diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32 (1): 193.

Throughout the application, each clinical trial report has two identifying numbers, one in the format 1218.xx and the other in the format Uxx-xxxx-xx. In this evaluation report, the 1218.xx format only is used.

The submission is in the CTD format and contained the following clinical information:

- A single newly submitted pivotal efficacy/safety study, 1218.36, supporting the addition of linagliptin to insulin with or without various combinations of other OHA.
- Six other efficacy/safety studies. Five of these support various aspects of the application for extension of indications; four of these (1218.40, 1210.43, 1218 .50 and 1218.52) have been previously evaluated but are now presented with final extension data; and one (1218.63) is newly presented. The sixth (1218.20) is the final 104 week report of a study evaluated for a previous submission to the TGA and is presented in support of an update to the clinical trials section unrelated to this application for extension of indications.
- Pooled safety analysis
- Literature references

2.2. Paediatric data

The submission did not include paediatric data. The claimed indications refer to adult patients only.

2.3. Good clinical practice (GCP)

All of the studies in the application comply with the established guidelines for GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

No studies providing evaluable analyses of PK data were included in the submission. PK measurements were nevertheless obtained in some of the included studies. Linagliptin concentrations in trough samples were obtained in pivotal Study 1218.36 but the results are not provided in the interim report included with this submission. It is stated that they will be provided in the final report. Trough linagliptin measurements were also obtained, with particular reference to level of renal dysfunction, in supporting studies 1218.43 and 1218.63, and are referred to in the relevant study summaries below.

3.2. Summary of pharmacokinetics

The limited PK data referenced in the previous paragraph is discussed below in relation to safety in the renally impaired population.

3.3. Evaluator's overall conclusions on pharmacokinetics

Conclusions are limited to the above referenced discussion on renal safety.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

No pharmacodynamic studies have been submitted with or are relevant to this application.

4.2. Summary of pharmacodynamics

Not applicable.

4.3. Evaluator's overall conclusions on pharmacodynamics

Not applicable. The pharmacodynamic action of linagliptin has been well characterised in previous submissions, particularly the initial registration application.

5. Dosage selection for the pivotal studies

As indicated above, a single dosing schedule of 5 mg once daily applies to all current indications for linagliptin and has been continued in the pivotal Study 1218.36 and all of the other studies in the submission.

6. Clinical efficacy

6.1. Pivotal efficacy study

6.1.1. Study 1218.36

6.1.1.1. Study design, objectives, locations and dates

This was an international multicentre, randomised, double-blind, parallel group, placebo-controlled study the object of which was, in T2DM patients with insufficient glycaemic control on basal insulin therapy, to investigate the efficacy and safety of add-on treatment with linagliptin 5 mg by comparison with placebo. The overall study design was quite simple, as shown below (Figure 1).

Figure 1. Study design

Although the objectives stipulate at least 52 weeks of double-blind treatment, the primary efficacy endpoint was determined at 24 weeks, up until which time the dose of basal insulin was to remain stable. After 24 weeks, it could be adjusted according to the clinical judgement of the investigator.

The study was conducted between August 2009 and February 2011 at 167 centres in 19 countries with a wide geographic distribution; Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan and the United States.

It should be noted that the report included in this submission is an interim report and only includes the data up until the 24 week time point.

6.1.1.1.1. Inclusion and exclusion criteria

Inclusion criteria: patients ≥18 years with type 2 diabetes mellitus (T2DM) who were being treated with subcutaneous basal insulin alone or in combination with metformin and/or pioglitazone; screening haemoglobin A1C (HbA1c) ≥7.0% and ≤10.0%.; body mass index (BMI) ≤45 kg/m^2. Permissible basal insulins included glargine, detemir and NPH.

The diagnosis of T2DM was confirmed by C-peptide measurement at screening. In the 12 week period prior to randomisation, insulin dose was to change by no more than 10% of the baseline value, and dosage of concomitant oral hypoglycaemic therapy was to remain unchanged.

Exclusion criteria were wide ranging. Important exclusions included uncontrolled fasting hyperglycaemia (>13.3 mmol/L), impaired hepatic function, a history of gastric bypass surgery, treatment with oral hypoglycaemic agents other than metformin or pioglitazone within the previous 3 months, and the use of systemic corticosteroid therapy.

6.1.1.1.2. Study treatments

Linagliptin 5 mg tablets for oral administration or matching placebo.

Compliance with treatment was measured by tablet counts and regarded as satisfactory if the ratio of actual/expected consumption was between 0.80 and 1.20 (80%-120%). Up to the point of the efficacy analysis at 24 weeks, compliance was maintained at >95% in both linagliptin and placebo treatment groups.

6.1.1.1.3. Efficacy variables and outcomes

The main efficacy variables were:

- HbA1c
- Fasting plasma glucose (FPG)
- Proportion of subjects achieving target HbA1c levels of <7.0% or <6.5%.
- Weighted mean daily glucose. This was measured within the week prior to randomisation, the week prior to determination of the main efficacy parameter at Week 24, and the week prior to the end of treatment visit (usually Week 52). The measurement was derived from eight self monitored finger prick blood glucose levels over a single 24 hour period: before and 1-1.5 hours after each meal, prior to bed, and fasting the next morning, and calculated as the area under the plasma glucose curve (AUCG).

The primary efficacy outcome was the change from baseline in HbA1c after 24 weeks of double-blind therapy.

Other efficacy outcomes included:

- Proportion of subjects achieving HbA1c lowered by ≥0.5% from baseline.
- Use of rescue therapy; most commonly, increase in the basal insulin dose so that the change in insulin dose beyond Week 24 was an evaluable outcome.
- Change in body weight from baseline to Week 24.

6.1.1.1.4. Randomisation and blinding methods

As shown above (Figure 1), at the end of the two week placebo run-in period subjects were assigned to one of the two treatment groups. This was determined by a medication number issued by a computer-generated random sequence administered by interactive voice response system (IVRS) which ensured that both subjects and investigators remain unaware of the treatment group allocation of individual subjects. Following randomisation, each subject was issued with a medication kit, provided by the sponsor, bearing the corresponding medication number.

The randomisation code could be broken in emergency. This occurred 5 times during the study, an incidence insufficient to influence the results.

6.1.1.1.5. Analysis populations

Of 1848 subjects enrolled, 1263 were randomised in a 1:1 ratio to receive placebo (630) or linagliptin (633). 630 placebo and 631 linagliptin patients received study medication and of these, 133 (10.5%) (12.4% placebo, 8.7% linagliptin) discontinued study medication prior to the 24 week efficacy analysis. The most common reason for discontinuation was the occurrence of adverse events (AE) in 3.7% and 2.9% of the two groups respectively.

Of the treated subjects, 52% were male, and 80% White. Mean age was 60.0 years and mean baseline BMI similar in the two groups (placebo, 31.2; linagliptin, 30.8). 45.1% were from centres in Europe, 17.9% from North America and 25.9% South America.

Time since diagnosis of diabetes was >5 years in the majority (85.6%) of subjects, 1 to 5 years in 12.3%, and up to 1 year in 2.1%, with similar distribution of values between the linagliptin and placebo groups.

At baseline, 72.6% of subjects were taking metformin in addition to insulin, 6.6% metformin and pioglitazone, and 2.9% pioglitazone alone; 17.9% were on insulin alone, with no oral hypoglycaemics other than the double-blind study medication.

There was a significant incidence of impaired renal function as determined by estimated glomerular filtration rate (eGFR). 45.6% of treated subjects had mild renal impairment (eGFR 60 to <90 mL/min), 10.1% had moderate impairment (eGFR 30 to <60 mL/min), while 0.6% had severe or end-stage renal impairment (eGFR <30 mL/min).

6.1.1.1.6. Sample size

Sample size calculations are described below:

"*Based on a standard deviation of 1.2% for a change in HbA1c from baseline to 24 weeks, a total of 284 patients per treatment group would be sufficient to achieve a power of 93% to detect a 0.35% difference in HbA1c change from baseline between the treatment groups. The sample size in this trial with 600 patients in each treatment group was chosen to fulfill the regulatory requirements of the whole program to detect AEs in treated patients across trials.*"

With regard to efficacy, therefore, the numbers randomised were more than double the required sample size as described above.

6.1.1.1.7. Statistical methods

The outcome for the primary endpoint (24 week HbA1c) was determined as a superiority analysis using an Analysis of co variance (ANCOVA) model with treatment, concomitant oral antidiabetic therapy, and baseline renal function impairment category as fixed classification effects, and baseline HbA1c as covariate.

Secondary endpoints were determined by exploratory ANCOVA. For use of rescue medication (change in insulin dose after Week 24), logistic regression and Kaplan-Meier analysis were used.

Statistical analyses were performed on the full analysis set (FAS), which consisted of all treated subjects having a baseline and at least one on-treatment HbA1c value (n=1235), with last observation carried forward (LOCF) applied to subjects with missing data. Analyses were also performed on subsets of FAS completers consisting of all subjects who completed a lease 149 days of randomised treatment and had a HbA1c measurement at Week 24 (n=1127); and a per protocol set (PPS), a subset of the FAS comprising all those without an important protocol violation impacting on efficacy (n=1120).

6.1.1.1.8. Participant flow

There is no included diagram to illustrate this for the entire study, bearing in mind that the report is submitted as an interim analysis giving the 24 week data only. Disposition of patients up until the cut-off date for this interim analysis is shown below (Table 1).

Table 1. Patient Disposition

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			1848
Randomised			1343
Treated[1]	630 (100.0)	631 (100.0)	1261 (100.0)
Not prematurely discontinued trial medication	552 (87.6)	576 (91.3)	1128 (89.5)
Prematurely discontinued trial medication	78 (12.4)	55 (8.7)	133 (10.5)
Adverse event	23 (3.7)	18 (2.9)	41 (3.3)
Study disease worsening	4 (0.6)	0 (0.0)	4 (0.3)
Other disease worsening	1 (0.2)	3 (0.5)	4 (0.3)
Other AE	18 (2.9)	15 (2.4)	33 (2.6)
Lack of efficacy[2]	11 (1.7)	1 (0.2)	12 (1.0)
Non-compliance to protocol	3 (0.5)	5 (0.8)	8 (0.6)
Lost to follow-up	7 (1.1)	10 (1.6)	17 (1.3)
Refused to continue trial medication	21 (3.3)	13 (2.1)	34 (2.7)
Other reason	13 (2.1)	8 (1.3)	21 (1.7)

[1] In all tables 'treated' refers to treatment with randomised study drug
[2] Includes patients who discontinued due to hyperglycaemia

Of those enrolled, 72.7% were randomised. Of those randomised and treated, 89.5% completed the 24 week treatment period (87.6% placebo, 91.3% linagliptin).

6.1.1.1.9. Major protocol violations/deviations

Predefined protocol violations (PVs) occurred in 9.4% of placebo and 9.2% of linagliptin subjects. Those with the greatest frequency involved concomitant medication, particularly insulin. A higher proportion of placebo than linagliptin subjects (2.7% versus 1.4%) underwent an unauthorised increase in insulin dose between 0-24 weeks, whereas the reverse situation of an unauthorised decrease occurred less commonly in the placebo group (1.3% versus 3.0%). This would obviously factor if anything against a positive finding in favour of linagliptin. Other PVs involved incorrect treatment allocation (again, not favouring linagliptin) in 2 subjects and failure to meet entrance criteria in terms of associated disease in 4 subjects. There were no PVs which would have favoured a false-positive finding in favour of the study drug.

6.1.1.1.10. Baseline data

A summary of baseline data for the FAS, including distribution of use of concomitant antidiabetic therapy, is shown below (Table 2).

Table 2. Baseline data for FAS

	Placebo	Linagliptin	Total
Number of patients, N (%)	617 (100.0)	618 (100.0)	1235 (100.0)
Baseline HbA_{1c} [%]			
Mean (SD)	8.29 (0.85)	8.31 (0.85)	8.30 (0.85)
Baseline HbA_{1c}, categorical, N (%)			
<7.0%	24 (3.9)	23 (3.7)	47 (3.8)
7.0% to <8.0%	204 (33.1)	218 (35.3)	422 (34.2)
8.0% to <9.0%	249 (40.4)	235 (38.0)	484 (39.2)
≥ 9.0%	140 (22.7)	142 (23.0)	282 (22.8)
Baseline fasting plasma glucose [mg/dL]			
Mean (SD)	151.3 (46.4)	147.2 (46.0)	149.3 (46.2)
Concomitant oral antidiabetic drugs, N (%)			
No concomitant OADs	102 (16.5)	97 (15.7)	199 (16.1)
Metformin only	464 (75.2)	469 (75.9)	933 (75.5)
Pioglitazone only	6 (1.0)	6 (1.0)	12 (1.0)
Metformin + pioglitazone	45 (7.3)	46 (7.4)	91 (7.4)

Mean basal insulin dose was 40.1 and 41.6 units in the placebo and linagliptin groups respectively.

Comment: throughout the tables and in some but not all of the text in the report, plasma glucose measurements are given in mass (described somewhere in the summary documents as "conventional") as opposed to SI units. The reader may convert these to SI units by dividing by 18 so that in this case the overall baseline FPG was 8.3 mmol/L.

6.1.1.2. Results for the primary efficacy outcome

The results for change in HbA1c from baseline to Week 24 on the FAS (LOCF) are shown below (Table 3).

Table 3. Results for change in HbA1c to Week 24. FAS.

	Placebo	Linagliptin
Number of patients analysed	617	618
Baseline HbA_{1c} [%]		
Mean (SE)	8.29 (0.03)	8.31 (0.03)
HbA_{1c} at Week 24 [%]		
Mean (SE)	8.32 (0.04)	7.69 (0.04)
Change from baseline HbA_{1c} at Week 24 [%]		
Mean (SE)	0.04 (0.04)	-0.62 (0.04)
Adjusted[1] mean (SE)	0.07 (0.08)	-0.58 (0.08)
Comparison vs. placebo (difference linagliptin - placebo) [%]		
Adjusted[1] mean (SE)		-0.65 (0.05)
95% Confidence interval		-0.74, -0.55
p-value		<0.0001

[1] Model includes baseline HbA_{1c}, treatment, concomitant oral anti-diabetics, and baseline renal function impairment category

Superiority of linagliptin over placebo is demonstrated. There was no placebo effect and the between treatment difference of 0.65% in HbA1c is clinically significant.

A secondary analysis of this outcome on the PPS, which excludes the protocol violators mentioned above, shows a similar result with a treatment difference in HbA1c also of 0.65%.

Of considerable interest in view of the proposed indication, which claims efficacy of linagliptin together with insulin with or without a variety of other oral hypoglycaemic agents, is the influence of concomitant antidiabetic therapy on the treatment effect. As mentioned above, such treatments were included in the statistical analysis model, along with renal impairment

category, as fixed classification effects which enable the performance of appropriate sub-analyses. These were presented in a table in the study report. This table was rather complex and only the relevant sections are reproduced below (Table 4).

Table 4. Effect of Concomitant antidiabetic therapy and renal function impairment

Factor	Estimate	Standard Error	95% CI LL	95% CI UL	p-value
Concomitant OADs by treatment group interaction					0.6360
No concomitant OADs: Linagliptin - Placebo	-0.53	0.13	-0.78	-0.28	<0.0001
Metformin only: Linagliptin - Placebo	-0.70	0.09	-0.87	-0.52	<0.0001
Pioglitazone only: Linagliptin - Placebo	-0.79	0.50	-1.76	0.19	0.1154
Metformin + Pioglitazone: Linagliptin - Placebo	-0.74	0.19	-1.12	-0.36	0.0001
Renal function impairment cat. by treatment interaction					0.6643
eGFR>=60: Linagliptin - Placebo	-0.65	0.14	-0.92	-0.38	<0.0001
eGFR<60: Linagliptin - Placebo	-0.72	0.19	-1.11	-0.34	0.0002

A statistically and clinically significant level of treatment difference between linagliptin and placebo in combination with insulin is preserved in the presence or absence of metformin. A numerical difference in HbA1c response of 0.79% is also preserved in the pioglitazone only group, but this is not statistically significant, attributable to the very small number in this category (6 treated with placebo, 6 linagliptin).

Comment: This is not a comparison of the efficacy of linagliptin by comparison with metformin in combination with insulin. The important finding is that the size of the treatment effect when linagliptin is added to insulin in the presence of metformin (HbA1c reduction 0.70%) is not reduced by comparison with its being given to patients on insulin alone (0.53%); in fact it is greater although whether that difference is statistically significant cannot be judged. It is also evident that the presence of pioglitazone in the treatment combination does not impair the efficacy of linagliptin.

The data also show that linagliptin added to insulin remains effective in the presence of moderate renal dysfunction, with no change in the size of the treatment effect on HbA1c (-0.72%, -0.65%).

6.1.1.3. Results for other efficacy outcomes

6.1.1.3.1. Response by HbA1c category

The proportion of subjects achieving predefined HbA1c categories below 7.0% and below 6.5%, both overall and according to baseline HbA1c category, are shown below (Table 5).

Table 5. Proportion of subjects achieving predefined HbA1c categories below 7.0% and below 6.5%. Overall and according to baseline HbA1c category.

	Placebo		Linagliptin	
	n[1] (%)	N[2]	n[1] (%)	N[2]
Response criterion				
HbA_{1c}<7.0%	56 (9.1)	617	134 (21.7)	618
Among patients with baseline HbA_{1c} ≥7.0%	48 (8.1)	593	116 (19.5)	595
HbA_{1c} <6.5%	10 (1.6)	617	50 (8.1)	618
Among patients with baseline HbA_{1c} ≥6.5%	9 (1.5)	615	48 (7.8)	616
HbA_{1c} reduction from baseline ≥0.5%	137 (22.2)	617	333 (53.9)	618

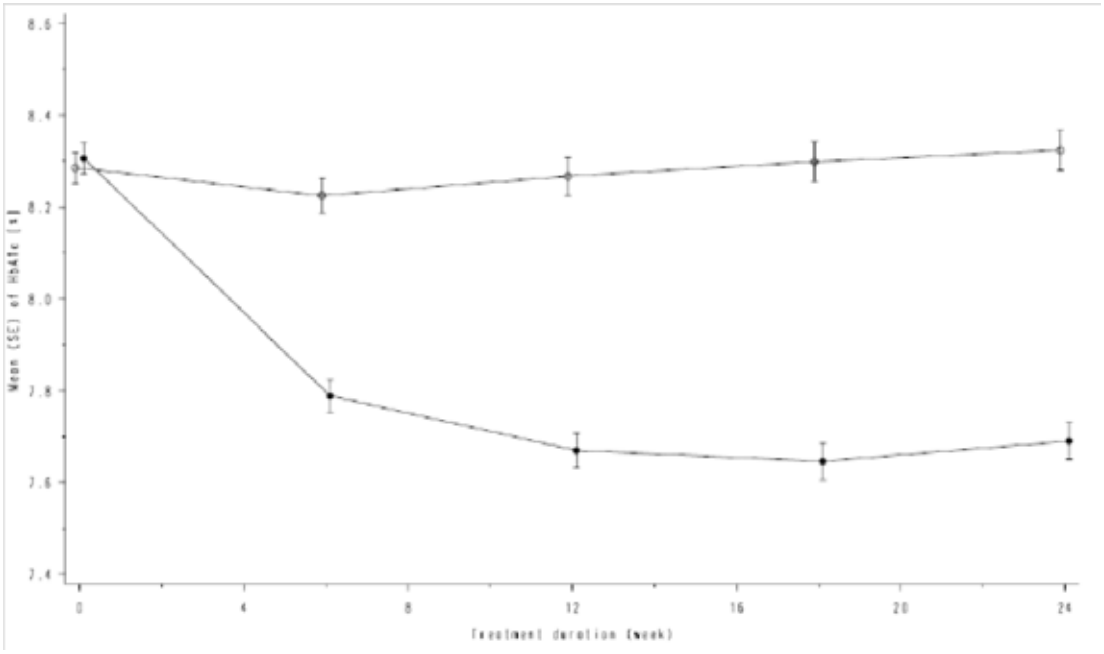
[1] Number of patients with a response
[2] Number of patients analysed

Statistical analysis of these data was provided in the study report. The odds ratios (linagliptin to placebo) for subjects with the relevant predefined baseline category achieving HbA1c below 7.0% and below 6.5% were 3.147 and 6.043 respectively and for achieving a HbA1c reduction from baseline of 0.5% or greater, 4.279, all ratios being highly significant (p<0.0001).

6.1.1.3.2. Change in HbA1c over time

HbA1c values for the placebo group (open circles, upper line) and linagliptin group (closed circles, lower line) over the treatment period 0-24 weeks is shown below (Figure 2).

Figure 2. HbA1c values for the placebo group (open circles, upper line) and linagliptin group (closed circles, lower line) over the treatment period 0-24 weeks.



The treatment effect in HbA1c is established at 12 weeks and remains undiminished at 24 weeks.

Although determination of the primary efficacy parameter was defined at 24 weeks and rescue therapy was permitted after that, findings regarding subsequent maintenance of the treatment effect on HbA1c over the remaining 28 weeks of the study are clearly important. In this interim report, there is no statistical analysis of data beyond 24 weeks but some descriptive statistics were found in supplementary table. At Week 40, HbA1c change from baseline was -0.76% in the linagliptin group (n=264) by comparison with -0.12% in the placebo group (n=220); and at Week 52, -0.72% (n=132) by comparison with -0.16% (n=94).

Comment: although the final 52 week report of the study will be of interest, the above data are reasonably convincing that the treatment effect is maintained for the full duration of the study, particularly given the large sample sizes.

6.1.1.3.3. Change in fasting plasma glucose (FPG)

As noted above, FPG data are presented in the study report in "conventional" units; in the following section copied from the study report, the evaluator inserted corresponding standard (SI) unit values in bold. '*At baseline, mean FPG values were comparable for both treatment groups (151.29 mg/dL **(8.41 mmol/L)** placebo; 147.13 **(8.17 mmol/L)** mg/dL linagliptin). After 24 weeks of randomised treatment, the adjusted mean change in FPG from baseline was 2.93 mg/dL **(0.16 mmol/L)** for the placebo group and -8.32 mg/dL **(-0.46 mmol/L)** for the linagliptin group. The difference in the adjusted mean change in FPG between placebo and linagliptin was -11.25 mg/dL **(-0.63 mmol/L)** (95% CI: -16.14 **(-0.90)**, -6.36 **(-0.35)**; p<0.0001)."*

Superiority of linagliptin over placebo in the reduction in FPG from baseline was demonstrated by statistical analysis of these data.

Comment: Although relatively small, the reduction in FPG attributed to the study treatment is probably of clinical significance. Further data in the study report show this response

to be quite variable over time. This is probably due to variations in the dosage of basal insulin, which will tend to affect FPG more than other parameters. The further analyses of FPG data provided do not add significantly to the overall findings of study and are not presented in detail particularly in view of their presentation in conventional units.

6.1.1.3.4. Weighted mean daily glucose

The study report states that at the cut-off date for the interim analysis, data for this parameter were only available for less than 10% of subjects, so that data analysis was not feasible.

Comment: For the purpose of this evaluation report, the absence of this data is not felt to be critical.

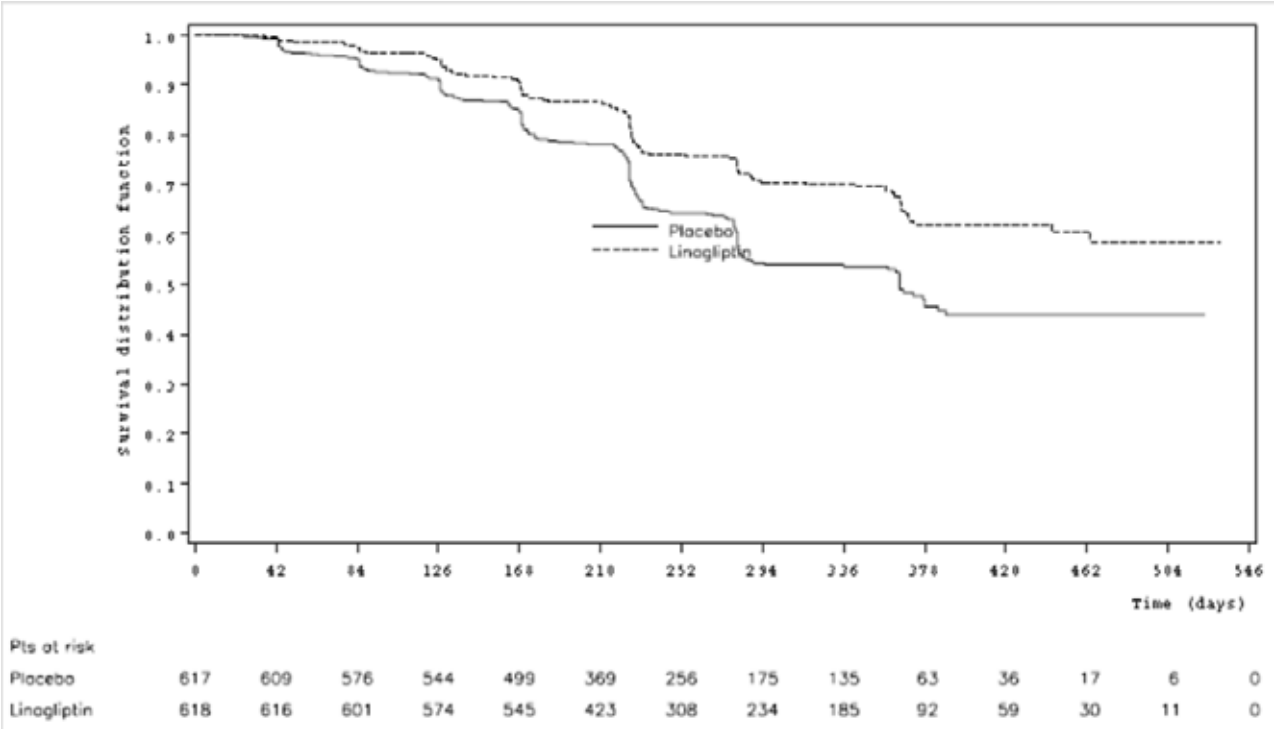
6.1.1.3.5. Use of rescue treatment

According to the protocol, the first choice of rescue therapy was to be the adjustment of basal insulin therapy. The prescribed dosage was left to the discretion of the study investigator. An increase in prescribed insulin dose of more than 10% of the baseline value was considered as rescue therapy. The study report indicates that "*in very rare cases*", adjustment of background therapy or addition of another oral antidiabetic medication would be appropriate.

The proportion of patients requiring the use of rescue medication during the first 24 weeks of randomised treatment was greater in the placebo group (19.8%) than in the linagliptin group (12.6%). The associated odds ratio of using a rescue medication for patients treated with linagliptin compared with placebo was 0.572 (95% CI: 0.418, 0.782; p=0.0005). This difference was mainly attributable to changes in the baseline insulin dose of more than the permitted 10%, details of which are provided in the study report. Increases in other antidiabetic medications occurred up until Week 24 in only 0.3% of both placebo and linagliptin patients.

A Kaplan-Meier plot showing the time related incidence of first use of rescue therapy (principally increase in insulin dose) for the entire duration of the study is shown below (Figure 3).

Figure 3. Kaplan-Meier plot of the time related incidence of first use of rescue therapy.



Comment: the above data includes approximately one quarter of the study population completing 52 weeks of double-blind therapy, with a progressive protection from the need for rescue therapy evident in the linagliptin group. Taken together with the maintenance of improved HbA1c in the preliminary 52 week data noted above, this finding supports maintenance of the therapeutic effect of linagliptin in this setting over the first year of treatment.

6.1.1.3.6. Hypoglycaemic episodes

The incidence of hypoglycaemic episodes was monitored throughout the 24 week randomised period. Not surprisingly for patients treated with insulin, there was a significant incidence in both the placebo (24.0%) and linagliptin (27.4%) groups. The small difference is consistent with the improved control in the linagliptin group and is not directly attributable to the study medication.

6.1.1.3.7. Change in body weight

Mean change in body weight at Week 24 was 0.39 kg in the placebo group and -0.15 kg in the linagliptin group; and at Week 52 on a smaller number of patients, -0.38 kg and -0.67 kg respectively. The study report notes that these data are slightly skewed by 2 patients in the placebo group at the same centre with recorded weight increases of >100 kg (obviously erroneously reported). The median changes in weight are close to 0 for both groups and there is clearly no significant effect related to study treatment.

6.1.2. Other efficacy studies

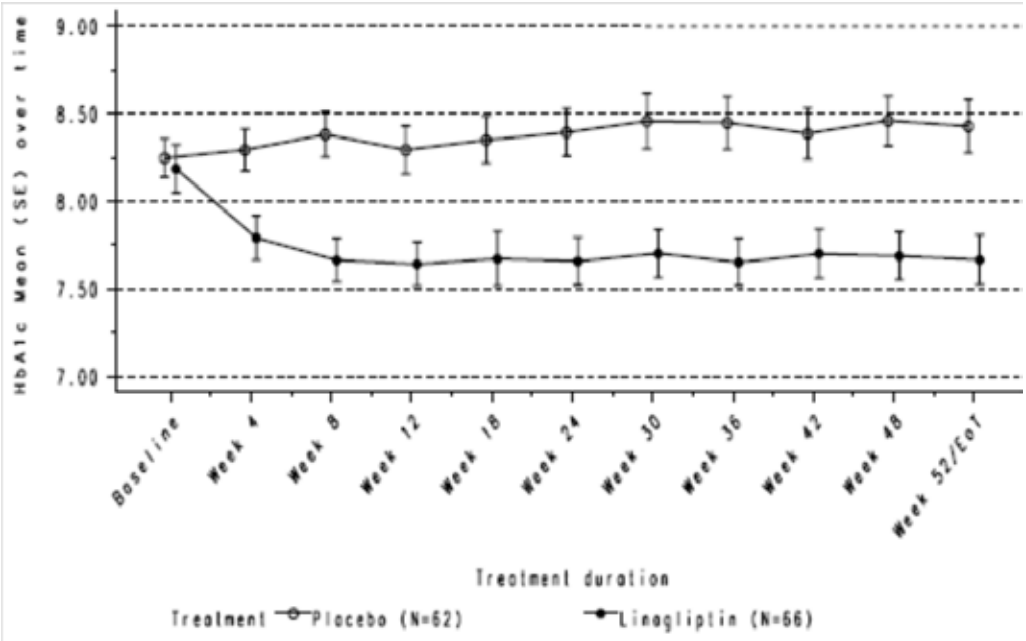
6.1.2.1. Study 1218.43

This study was evaluated for a previous TGA submission. Although the sponsor's letter of application and the clinical overview state that the "*final 52 week data are now presented*", these data were available for the previous evaluation.

The study was conducted on a population of T2DM patients with severe chronic renal impairment defined by eGFR <30 ml/min and a wide range of impairment of glycaemic control (Hb A1c >7.0 to ≤10.0%) who were being treated with a wide range of diabetes therapy, the inclusion criterion reading: '*insulin or any combination of insulin, sulphonylurea or glinides as monotherapy and pioglitazone or any other antidiabetics excluding DPP-4 inhibitors other than linagliptin*.' The previous evaluator made the comment that the study was of little relevance to the application for a FDC containing metformin which is contraindicated in renal failure.

Some 133 subjects were randomised to either linagliptin (n=68) or placebo (n=65). Other pre-randomisation diabetes therapy was to remain unchanged for the first 12 weeks of the study, after which it could be adjusted by the investigator; nevertheless the primary efficacy parameter in this final report is the change in HbA1c from baseline after 52 weeks of double-blind therapy. The result for the treatment difference (mean, 95% CI) was -0.72 (-1.03, -0.41)%, demonstrating superiority of linagliptin over placebo (p<0.0001). A treatment response of this size was evident after 12 weeks (the study report refers to change at Week 12 having been the primary endpoint in a previous interim report) and was preserved for the duration of the study, as shown below (Figure 4).

Figure 4. HbA1c response at baseline and throughout the study.



The treatment effect attributable to linagliptin persisted between Weeks 12-52 despite changes to background medication which were, as indicated above, permissible at that stage. Between Weeks 12-52 more placebo subjects (51.8%) than linagliptin subjects (39.3%) had at least one change in the background therapy, most frequently an increase in insulin dose. During this period, 24/56 placebo and 22/61 linagliptin subjects had their insulin dose changed: the mean change for these placebo subjects was an increase of 9.7% whereas for the linagliptin subjects there was a mean decrease of 14.3%. Also of note, 3 linagliptin subjects taking sulphonylurea had the drug withdrawn. All of these therapy changes would act towards diminishing the treatment effect of linagliptin evident in Figure 4.

The relevance of this study to the present submission is that it demonstrates a clinically significant and enduring glycaemic response to linagliptin in the setting of a variety of background diabetes therapy, including use in combination with insulin, in the presence of severe renal impairment. The sponsor's Clinical Overview cites this study in support of both proposed new indications, use with insulin (with or without other OAD) and use as monotherapy. The types of other antidiabetic medications being used by the study subjects is therefore of particular interest and is shown below (Table 6).

Table 6. Other antidiabetic medications used by study participants

	Placebo	Linagliptin	Total
Number of patients	62 (100.0)	66 (100.0)	128 (100.0)
Number of antidiabetic background drugs [N (%)]			
1	51 (82.3)	46 (69.7)	97 (75.8)
2 or more	11 (17.7)	20 (30.3)	31 (24.2)
Antidiabetic background drugs at enrolment [N (%)]			
Insulin only	43 (69.4)	37 (56.1)	80 (62.5)
Metformin only	0	0	0
Sulphonylurea only	7 (11.3)	9 (13.6)	16 (12.5)
Glitazone only	1 (1.6)	0	1 (0.8)
Alpha-glucosidase inhibitor only	0	0	0
Glinide only	0	0	0
GLP-1 agonist only	0	0	0
Other antidiabetic agents only	0	0	0
Insulin + Metformin	0	1 (1.5)	1 (0.8)
Insulin + Sulphonylurea	4 (6.5)	9 (13.6)	13 (10.2)
Insulin + Glitazone	1 (1.6)	3 (4.5)	4 (3.1)
Insulin + Glinide	2 (3.2)	0	2 (1.6)
Insulin + Other antidiabetic agents	0	1 (1.5)	1 (0.8)
Metformin + Sulphonylurea	0	1 (1.5)	1 (0.8)
Sulphonylurea + Glitazone	1 (1.6)	2 (3.0)	3 (2.3)
Sulphonylurea + Alpha-glucosidase inhibitor	0	1 (1.5)	1 (0.8)
Alpha-glucosidase inhibitor + Glinide	0	1 (1.5)	1 (0.8)
Insulin + Metformin + Sulphonylurea	0	1 (1.5)	1 (0.8)
Insulin + Sulphonylurea + Glitazone	1 (1.6)	0	1 (0.8)
Metformin + Sulphonylurea + Glitazone	2 (3.2)	0	2 (1.6)

The majority of the subjects (50/62 placebo, 52/66 linagliptin) were using insulin, mostly alone or otherwise most commonly in combination with sulphonylurea. In one of these severely renally impaired subjects, insulin was being used inappropriately together with metformin. 12/62 placebo and 23/66 linagliptin subjects were using sulphonylureas, with similar proportions alone or in combination with insulin (and again, one in combination with metformin). The usage of other OAD or combinations thereof was minimal, in the range 1-3 subjects per treatment group. There were no subjects who were not taking antidiabetic therapy other than the double-blind study therapy, so the relevance of this study to the proposed monotherapy indication is limited.

Comment: No sub-analyses were performed of HbA1c change by class of background therapy. It is evident from the above table that the numbers of subjects on specific therapies other than insulin would be insufficient to demonstrate significant change. While the effect of linagliptin in combination with insulin alone has not been specifically tested, the dominance of insulin amongst the background therapies makes it reasonable to assume that linagliptin is effective in combination with insulin in this renally impaired group of T2DM patients.

Of note, and not mentioned in the original CER, is that a small proportion of subjects did not continue to meet the criterion for severe renal impairment of eGFR <30 mL/min at the time of randomisation. Subjects were selected for randomisation on the basis of meeting inclusion criteria including eGFR as above, calculated using a standard formula. When this was repeated at the baseline visit immediately prior to commencement of double-blind therapy, 14 placebo and 5 linagliptin subjects showed values that no longer met this criterion. The difference is attributed to the second calculation being carried out using the modification of diet in renal disease (MDRD) formula but could well be contributed to by other factors including better treatment compliance in study conditions and random variation. The differences are not great; in 12 of the 19 subjects, eGFR remained <35 mL/min and the highest observed value was 42.9 mL/min. For practical clinical purposes the subjects would still be classified as being in severe renal failure and the study investigators' decision to not regard these as protocol violations is supported.

Limited PK data were obtained in the study. The sponsor's summary is as follows: 'Linagliptin trough concentrations were stable over time and, in patients with severe renal impairment, the

lowest gMean levels were observed at Week 48 (6.78 nmol/L; n=40), and the greatest gMean levels were observed at Week 30 (8.80 nmol/L; n=41).' It is further stated that these levels are similar to those obtained in normal subjects or subjects with mild or moderate renal impairment in previous studies at this dosage (5 mg daily) and support the proposal that no dose adjustment is required in patients with any degree of renal impairment. This was accepted in the CER for the original application.

6.1.2.2. Study 1218.63

This newly submitted randomised, double-blind, placebo-controlled, parallel group study examines the efficacy and safety of linagliptin 5 mg daily over 24 weeks in T2DM patients aged ≧70 with insufficient glycaemic control (HbA1c ≧7.0%) despite treatment with metformin and/or sulphonylurea and/or insulin.

The study was carried out at 33 sites in 5 countries (Australia, Canada, Denmark, the Netherlands and Sweden) between March 2010 and June 2011.

6.1.2.2.1. Study population

Of 377 enrolled subjects, 241 were randomised in 2:1 ratio, 162 to linagliptin and 79 to placebo. Of these, 160 and 78 respectively were analysed for the primary endpoint, change in HbA1c at 24 weeks of double-blind treatment.

6.1.2.2.2. Inclusion and exclusion criteria

Age and HbA1c criteria are given above. Patients of either gender with a diagnosis of T2DM were eligible if dosage of metformin and/or sulphonylurea was unchanged for 8 weeks prior to informed consent, and if on insulin the dose (basal only, taken up to 2 times daily) had not varied within that period by more than 20% of the baseline value at randomisation.

Exclusion criteria included a blood glucose of >13.3 mmol/L after overnight fast during the placebo run-in, a history of treatment with OHA other than metformin or sulphonylurea during the 3 months prior to the trial, treatment with rapid acting or premixed insulin and a range of disease and therapy based exclusions as would be anticipated for this disease and age group based population.

6.1.2.2.3. Statistical methodology

An ANCOVA model was used with treatment and prior use of insulin as fixed classification effects and baseline HbA1c as linear covariate, to test the hypothesis of superiority of linagliptin 5 mg over placebo. The calculations to describe appropriate sample size are summarised as follows in protocol amendment document 16101 which was included with the study report:

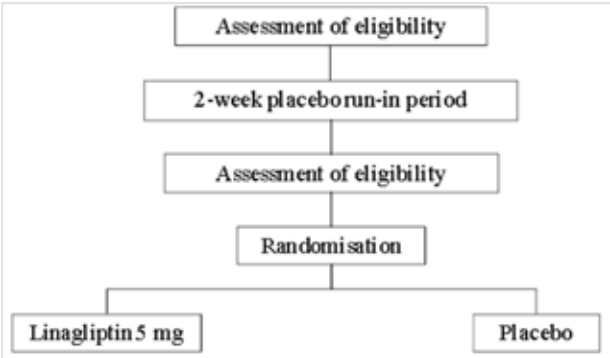
'Two phase 3 linagliptin trials 1218.16 and 1218.17 showed a standard deviation for HbA1c change from baseline after 24 weeks of treatment of between 0.9 and 1.1. From the same source, the mean baseline HbA1c of around 8% was observed. Therefore, for this sample size calculation a common SD in HbA1c of 1.1 and baseline HbA1c of 8% is assumed.

A number of 77 evaluable patients in the placebo group and 154 in the linagliptin group are required to achieve a power of 90% to detect a 0.5% difference in HbA1c change from baseline using a 2-sided test with α=0.05. To account for potential drop-outs 5% will be added to each treatment group, resulting in a total sample size of 243 randomised patients.'

6.1.2.2.4. Participant flow

The study design is shown below (Figure 5).

Figure5. Participant flow



With reference to the above diagram, 377 subjects enrolled and presented for assessment and of these 253 entered the two-week placebo run-in period. Of these, 241 were randomised and received either linagliptin (162) or placebo (79) as study treatment. Exclusions prior to randomisation were based on various aspects of the entry criteria, most commonly, and perhaps surprisingly, failure to meet the criterion for HbA1c ≧7.0% (97/136 excluded subjects).

Of the randomised subjects, 47.3% were studies in European centres, 29.0% in Canada, and 23.7% in Australia.

Randomisation was stratified by baseline HbA1c level and by use of insulin prior to the study. Most subjects (81.3%) had baseline HbA1c <8.5%, with the remainder being more poorly controlled. Likewise most (79.7%) had not used insulin prior to the study. The outcome of the stratification appears very satisfactory, with each of the four resulting substrata being distributed close to 2:1 linagliptin: placebo.

Of those randomised, 146/162 (90.1%) of linagliptin and 74/79 (93.7%) of placebo treated subjects completed 24 weeks of double-blind medication. The greater number of withdrawals in the linagliptin group is accounted for by a high incidence of adverse events leading to discontinuation which occurred principally in centres in Denmark and the Netherlands. All AE leading to discontinuation were reviewed in the study report. Two such events of depressed mood and insomnia in the placebo and linagliptin groups respectively were considered drug-related, although this seems unlikely. The remainder appears from the descriptions to be incidental conditions occurring with relatively high frequency in this age group.

Mean exposure to study medication was 159.7 days in the linagliptin and 163.8 days in the placebo groups respectively. In the linagliptin group, cumulative exposure was 70.9 patient years.

6.1.2.2.5. Population demographics

Of the randomised subjects, 68.5% were males and 96.7% White. Mean age was 74.9 years, with 44.4% of subjects being >75 years. Mild renal impairment (eGFR 60 to ≤90) was present in 51.9%, and moderate (eGFR 30 to ≤60) in 25.7%. 1.2% of subjects had severe renal impairment. Metformin was being used by 83.1% of linagliptin and 88.5 % of placebo subjects, and sulphonylurea by 58.8% and 55.1% respectively

6.1.2.2.6. Efficacy results

Analysis of the primary efficacy parameter, change in HbA1c from baseline to Week 24, was carried out on the FAS, which excluded only 1 placebo and 2 linagliptin subjects, with LOCF. The results are shown below (Table 7).

Table 7. Change in HbA1c from baseline to Week 24. FAS.

	Placebo	Linagliptin
Number of patients	78	160
Number of patients analysed	78	160
Baseline		
Mean (SE)	7.70 (0.08)	7.82 (0.06)
Change from baseline		
Mean (SE)	0.02 (0.08)	−0.67 (0.05)
Adjusted[1] mean (SE)	0.04 (0.07)	−0.61 (0.06)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted[1] mean (SE)		−0.64 (0.08)
95% confidence interval		(−0.81, −0.48)
p-value		<0.0001

[1] Model includes continuous baseline HbA_{1c}, prior use of insulin, and treatment
SE = Standard error

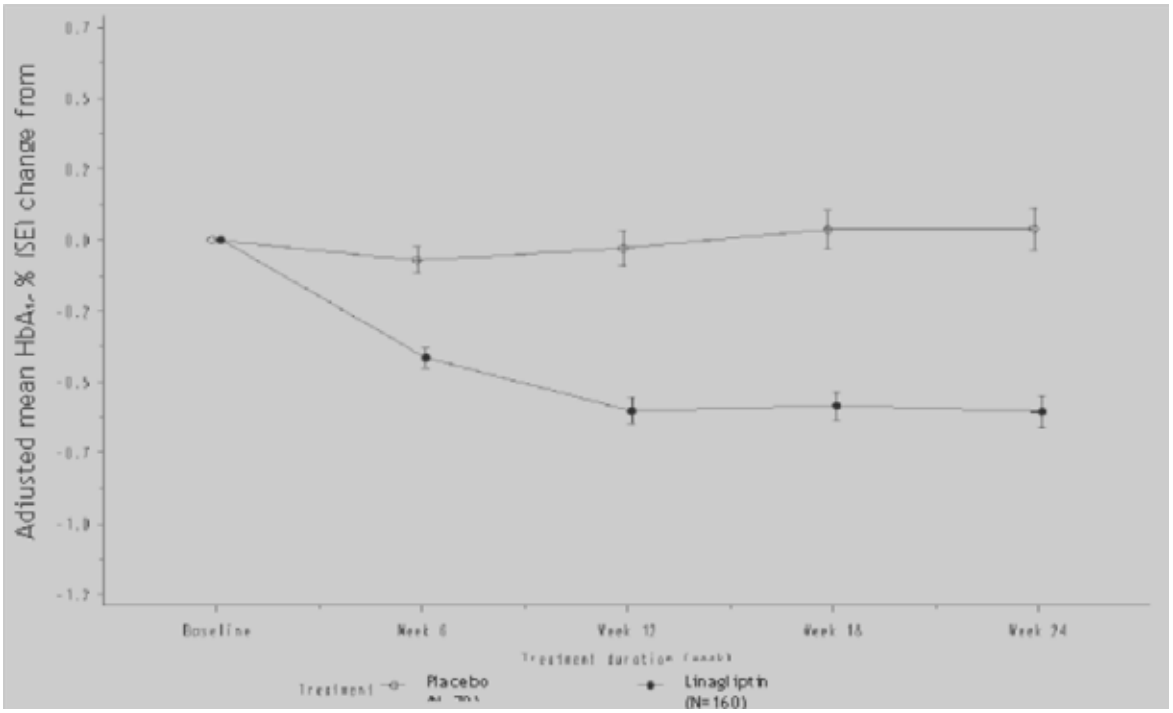
The treatment difference in HbA1c between linagliptin and placebo of 0.64% is clinically significant. As indicated above, the ANCOVA model used included prior insulin use and baseline HbA1c as covariates. In this model, the size of the treatment effect was shown to be not significantly different between those using and not using insulin. Baseline HbA1c was also found not to be predictive of treatment response. The absolute values for the treatment effect are shown below for the following subgroups:

- Insulin use, alone or in combination: -0.66%
- Background treatment with metformin only: -0.49%
- Background sulphonylurea, with or without metformin: -0.72%
- Age <75 years: -0.58%
- Age 75 years or greater: -0.73%

These secondary outcomes confirm that in this age group the efficacy of linagliptin is preserved whether in combination with insulin or not and in combination with metformin and/or sulphonylureas and that its efficacy does not diminish with increasing age of the patient. The relatively low effect size in subjects whose only other treatment was metformin is noted but may be a chance finding as efficacy of this combination has been demonstrated in previous studies.

The treatment effect was evident at 12 weeks and sustained thereafter even though adjustment of background anti-diabetes therapy was permitted after 12 weeks, as shown below (Figure 5).

Figure 5. Treatment effect. Adjusted mean HbA1c % change. Baseline to Week 24.



In the overall study population, a HbA1c level below 7% was achieved at 24 weeks by 38.9% of linagliptin subjects by comparison with 8.3% of those taking placebo (adjusted odds ratio, 8.319 ($p<0.0001$). A reduction in HbA1c from baseline of at least 0.5% was achieved by 54.4% of linagliptin versus 12.8% of placebo subjects. This differential response was maintained in subjects with higher baseline HbA1c levels. Rescue therapy was also use less commonly in the linagliptin group, 14.1% versus 4.4%. Body weight changes were not significantly different between the two groups.

6.1.2.2.7. Hypoglycaemia

Study investigator defined episodes of hypoglycaemia occurred more commonly in the linagliptin group (39 subjects, 24.1%) than with placebo (13 subjects, 16.5%). In the study report where this data is presented, there is extensive discussion of logistic regressions carried out to assess associations of hypoglycaemia. Amongst the findings were that insulin as background therapy was associated with a significant decrease in the likelihood of hypoglycaemia (odds ratio 2.869), whereas subjects on metformin had much higher odds of experiencing an episode of hypoglycaemia.

Comment: these associations are quite the reverse of what clinical experience would expect, and appear most likely to be due to failure of the model to adequately account for level of glycaemic control. The overall distribution of hypoglycaemia is not surprising: particularly in patients on insulin, there is always a reciprocal relationship between level of glycaemic control and incidence of hypoglycaemia, and any other factor introduced into the equation such as diet, exercise or as in this case another diabetes medication, will increase the probability of hypoglycaemia.

6.1.2.2.8. Pharmacokinetic data

Trough plasma concentrations linagliptin in a subset of subjects at Week 24 were shown, by category of renal function in the study report. The mean (SD) values were as follows: for subjects with normal renal function (n=4), 5.67 (2.76) nmol/L; with mild renal impairment (n=20), 6.86 (2.60) nmol/L; and with moderate renal impairment (n=11), 7.21 (2.22) nmol/L.

6.1.2.3. Study 1218.50

This was a 2 part study of the efficacy and safety of monotherapy with linagliptin 5 mg in T2DM patients with intolerance or contraindication to metformin. Part 1 of this multicentre international study previously evaluated for TGA, consisted of an 18 week period of double-blind therapy in which linagliptin (151 randomised subjects) was compared with placebo (76 subjects). In the newly submitted Part 2, placebo subjects were switched to glimepiride and double-blind treatment, using a double dummy technique, continued for a further 34 weeks as a comparator controlled trial. The overall structure of the study was fully evaluated and the results for Part 1 presented in the original CER. These demonstrated superiority of linagliptin over placebo with an adjusted mean difference in HbA1c (95% CI) after 18 weeks of -0.57(-0.86, -0.29)%. A reduction in HbA1c from baseline of 0.5% or greater was achieved by 36.1% of linagliptin subjects by comparison with 17.8% of placebo subjects.

The study population for Part 2 (median age 57, 65% female, 71% White, median BMI 29), is closely aligned with the target population for the revised proposed indication in this submission: 93% of randomised patients were metformin intolerant due to gastrointestinal side-effects and 7% contraindicated due to renal impairment.

The results of Part 2 of the study were not available at the time of the previous evaluation and were included in the present submission. Of the subjects originally randomised, 137/151 of the original 5 mg linagliptin subjects continued their treatment at the commencement of Part 2 and 64/76 were switched from placebo to glimepiride which was started at 1 mg daily and titrated upwards at weekly intervals to a maximum of 4 mg, as in other studies in the sponsor's development plan which exclusively use this regimen as the sulphonylurea comparator. The titration was based on prespecified blood glucose targets and was not to be continued past Week 12. Blinding was maintained by double placebo, including dummy titration. Patients from the original linagliptin arm, together with their investigators, remain blinded as to their treatment allocation in Part 1.

Some 119/137 linagliptin and 58/64 glimepiride subjects completed Part 2 of the study. Reasons for premature discontinuation are shown below (Table 8).

Table 8. Reasons for premature discontinuation.

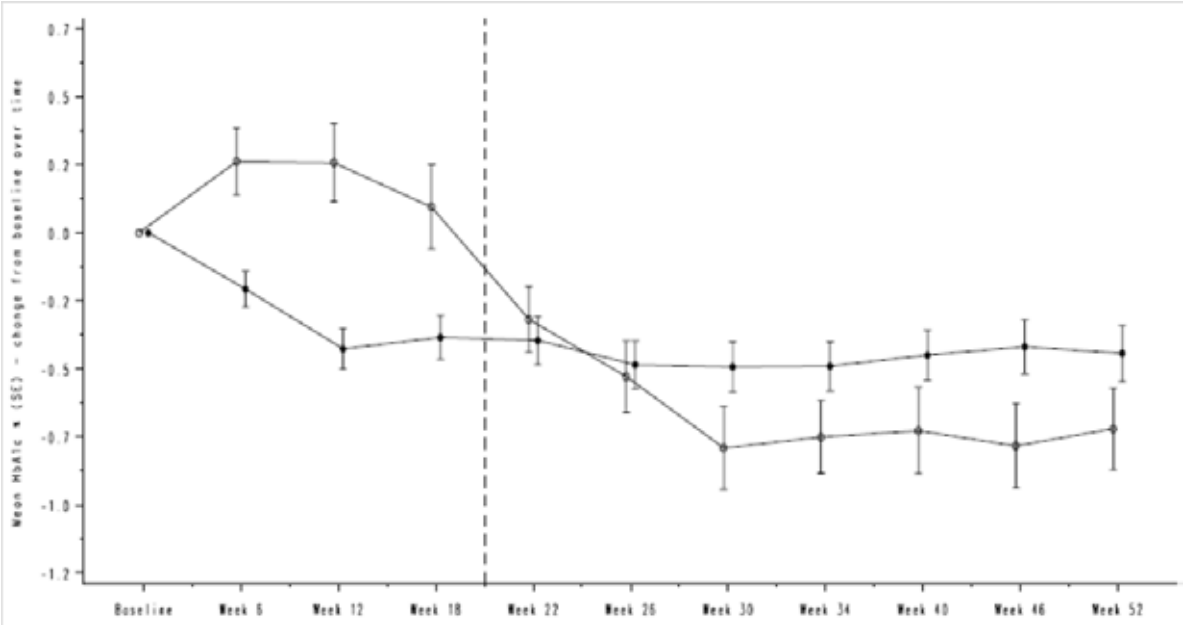
	Placebo / Glimepiride	Linagliptin	Total
	N (%)	N (%)	N (%)
Part 2 – Prematurely discontinued trial medication	6 (7.9)	18 (11.9)	24 (10.6)
Adverse event	1 (1.3)	3 (2.0)	4 (1.8)
Study disease worsening	0 (0.0)	1 (0.7)	1 (0.4)
Other disease worsening	0 (0.0)	1 (0.7)	1 (0.4)
Other	1 (1.3)	1 (0.7)	2 (0.9)
Lack of efficacy[2]	1 (1.3)	3 (2.0)	4 (1.8)
Non-compliance to protocol	0 (0.0)	5 (3.3)	5 (2.2)
Lost to follow-up	1 (1.3)	4 (2.6)	5 (2.2)
Refused to continue trial medication	1 (1.3)	3 (2.0)	4 (1.8)
Other reason	2 (2.6)	0 (0.0)	2 (0.9)

The % figures refer to a base of the number of subjects originally randomised in Part 1. "Lack of efficacy" includes hypoglycaemia. The apparent difference appears related to protocol issues and the figures do not suggest any bias in tolerability between the two arms of the study.

For the final study report (Part 1+ Part 2) the primary efficacy parameter remained the mean change from baseline in HbA1c at 18 weeks and the analysis of this was repeated on the FAS with adjustment for stratification factors (previous anti-diabetes therapy and reason for metformin intolerance) and baseline HbA1c, giving a result with 95% CI of -0.60 (-0.88, -0.32)%, slightly but not significantly different from the original estimate.

Surprisingly, no specific HbA1c endpoint was defined for Part 2 of the study; secondary endpoints are described as HbA1c reduction from baseline by visit over time, and the change from baseline in FPG by visit over time. Descriptive statistics are given for these parameters but there is no statistical analysis. A graphic display of the change in HbA1c in the two study groups over the entire study is shown below (Figure 6).

Figure 6. Mean HbA1c change from baseline over time



The symbols on this display are difficult to distinguish: the linagliptin group is the lower line which initially falls by Week 12 and then remains at a steady plateau until Week 52. HbA1c change from baseline rises initially for the placebo group and then falls between Weeks 18 and 30 following the switch to glimepiride, remaining constant thereafter.

Comment: the difficulty in reading this display is regretted, and the irregular progression of reference values on the vertical axis is not understood. Nevertheless it displays the fall in HbA1c between weeks 18 and 30 in the glimepiride group as being numerically greater than that which occurred for the linagliptin group during part 1 of the study.

Descriptive statistics provided for the treated set of subjects in the post-text tables show mean HbA1c for the linagliptin group to have fallen from 8.12% at baseline to 7.54% at 18 weeks, a fall of 0.58%; and for the placebo/glimepiride group, to have fallen from 7.99% at Week 18 to 7.18% at Week 30, a fall of 0.81%. This table also gives the overall change from baseline to Week 52 as being -0.44% for the linagliptin group and -0.72% for the placebo/glimepiride group.

A qualitatively similar pattern of change occurred in the change over time for FPG in the two groups.

Comment: The study report makes little comment about this pattern of change, except to repeatedly make the point that caution needs to be exercised in comparing the trends over time, due to different numbers of patients included the data at each time point. While this is a reasonable comment in general terms, there would have to be a major bias in the dropouts between the two groups to otherwise explain a strong visual impression that the reduction in HbA1c following the switch from placebo to glimepiride is greater than that following the commencement of linagliptin.

Use of rescue medication was similar between the two groups; 23.2% in the linagliptin group and 23.7% in the placebo/glimepiride group. There was a tendency for it to be used earlier in the

placebo/glimepiride group, that is, when the subjects were receiving placebo rather than glimepiride. This pattern is highly consistent with the progression of HbA1c values in the two groups shown above (Figure 6).

Incidence of hypoglycaemia was not defined as an outcome measure but in the safety evaluation a note is found that the incidence of AE attributed to hypoglycaemia during Part 2 was 7.8% for glimepiride and 2.2% for linagliptin.

Change in body weight; during Part 2, patients treated with glimepiride increased in weight on average 1.3 kg compared with a reduction of 0.2 kg in the linagliptin group.

6.1.2.4. Study 1218.40

This study was also evaluated in the previous submission. Conducted at 231 sites in 32 countries, it was a 78 week open-label extension to four studies which assessed the safety and efficacy of linagliptin 5 mg as monotherapy or in combination with other antidiabetic medications in T2DM. All four original studies (1218.15, 1218.16, 1218.17 and 1218.18) were evaluated in the CER for the initial Australian registration submission. In this trial, subjects who had received placebo in the original double-blind studies were switched to linagliptin 5 mg and referred to as the "new lina "group, whereas those who had been on active treatment were referred to as the "old lina" group.

The previous evaluation of 1218.40 concluded that the study confirmed long-term efficacy of linagliptin for up to 78 weeks in both linagliptin experienced and naive (new lina) patients ; that patients who had achieved good HbA1c control on linagliptin and other OHAs maintained good control; and that the addition of linagliptin to other OHAs resulted in additional clinically significant benefit which was maintained long-term. These conclusions were based on the final study report and there is no additional data in the version included with the current submission.

Of the 2124 enrolled subjects, 443 of the patients were from Study 1218.16 which was the pivotal study for linagliptin 5 mg monotherapy in the previous submission, and it is these who are of particular interest for this evaluation. The finding of the CER for the original submission was that linagliptin was shown to be superior to placebo by the primary efficacy outcome measure, the adjusted mean difference in change from baseline in HbA1c after 24 weeks double-blind therapy, which (with 95% CI) was -0.69 (-0.85, -0.53)% ($p<0.0001$). Treatment effect was greater in those with higher HbA1c at baseline and FPG was also significantly reduced.

The mean (SD) change in HbA1c from baseline to Week 78 for the old lina group in Study 1218.40 was +0.12(0.76)% and for the new lina group -0.49(0.85)%, a treatment difference for HbA1c of 0.61% which is clinically significant. This treatment difference applies to the new introduction of linagliptin 5 mg and continued for 78 weeks in the group of subjects previously treated with placebo but applies to the entire study population, the majority of whom were recruited from trials of combination therapy including sulphonylureas, metformin and pioglitazone. Unfortunately, no sub-analysis of the monotherapy patients specifically recruited from Study 1218.16 is referred to in the conclusions of the study report or could be found amongst the data.

6.1.2.5. Study 1218.52

This is a further study previously evaluated by the TGA. It was a randomised, double-blind, parallel group extension study to investigate the safety and efficacy of twice daily administration of the free combination of linagliptin 2.5 mg and metformin 500 mg or linagliptin 2.5 mg and metformin 1000 mg versus monotherapy with metformin 1000 mg twice daily over 54 weeks. It was an extension of Study 1218.46 which was the pivotal study for the submission.

The study appears to have no relevance to the current submission, was not mentioned in the letter of application except to list its inclusion, and is not drawn upon in the sponsor's Clinical

Overview or Summary of Clinical Efficacy documents which argue the case for the changes proposed to indications in this submission.

The version of the study report now submitted dated 10 November 2011 does contain the full 54 week data which were not available when the CER for the FDC submission was written. Previous interim reports were dated 20 September 2010 and 4 February 2011.

As noted in the original CER, there was no primary endpoint of the study but a descriptive analysis of several secondary endpoints including the change from baseline in HbA1c and the frequency of occurrence of a relative efficacy response defined as HbA1c lowering of at least 0.5%.

The changes in HbA1c from baseline and by visit for the three treatment groups are shown below (Table 9).

Table 9. The changes in HbA1c from baseline and by visit for the three treatment groups.

	met 1000 (N=170)		lina 2.5 + met 500 (N=225)		lina 2.5+ met 1000 (N=171)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
HbA_{1c} [%]						
Baseline	165	7.48 (0.99)	224	7.64 (1.04)	170	7.35 (1.12)
Week 6	162	7.36 (0.96)	208	7.34 (0.94)	167	7.08 (0.89)
Week 18	140	7.18 (0.84)	185	7.18 (0.88)	148	6.97 (0.89)
Week 30	125	7.08 (0.86)	165	7.05 (0.82)	135	6.86 (0.84)
Week 42	114	7.01 (0.82)	153	7.11 (0.80)	128	6.85 (0.83)
Week 54	101	7.01 (0.77)	133	7.15 (0.88)	118	6.88 (0.76)
Change in HbA_{1c} [%] from baseline						
To Week 6	157	-0.06 (0.41)	207	-0.24 (0.51)	166	-0.26 (0.59)
To Week 18	136	-0.08 (0.56)	184	-0.29 (0.79)	147	-0.34 (0.93)
To Week 30	121	-0.10 (0.82)	165	-0.41 (0.80)	134	-0.36 (0.87)
To Week 42	110	-0.14 (0.78)	152	-0.35 (0.80)	127	-0.28 (1.00)
To Week 54	98	-0.06 (0.77)	132	-0.28 (0.86)	117	-0.24 (0.91)

Corresponding mean values for change from baseline at 30 weeks for the three treatment groups (metformin 1000, linagliptin 2.5/metformin 500 and linagliptin 2.5 mg/metformin 1000 mg) were roughly similar at -0.19%, -0.46%, and -0.40% respectively.

For the set of patients who switched treatments for the extension trial (SWS) the mean change in HbA1c from baseline to Week 30 is stated in that CER to be more marked for the linagliptin 2.5 mg/metformin 1000 group at -1.25% than in the 2.5 mg/500 mg group, in which it was -0.89%, and the metformin only group (-0.58%). The corresponding values for these parameters in the SWS at 54 weeks in the current report are -0.96%, -0.63%, and -0.42% respectively. Thus, a treatment effect in favour of the linagliptin 2.5 mg/metformin 1000 mg group of >0.5% is maintained. Given that the CER defined this level of response as clinically significant in making its recommendations, it appears that the completed 54 week data do not materially alter the conclusions of the previous evaluation.

A further endpoint referred to in the original CER was the proportion of subjects achieving categorical efficacy responses of HbA1c either <7% or <6.5%. At 30 weeks as reported in the original CER, the <7% criterion was achieved by 61.8% of 2.5 mg/1000 mg subjects by comparison with 49.3% of metformin 1000 mg subjects. For the 54 week data now reported, these proportions are 56.8% and 50.5% respectively. The 6.5% criterion was achieved in the original 30 week report by 32.6% of the 2.5 mg/1000 mg subjects by comparison with 18.7% of the metformin only subjects, and in the 54 week data these proportions are now 34.7% and 21.8%. Again, these differences between the interim and final data do not appear materially different.

It is emphasised that this evaluation is making no conclusions about efficacy with regard to the treatment and control groups in this study but simply reporting the 54 week by comparison with interim 30 week data.

6.1.2.6. Study 1218.20

In the annotated tabular listing of contents, this study is not listed as having been evaluated previously but in fact was evaluated in the initial registration submission and its efficacy data are summarised on page 4 of the existing approved PI on the TGA website. The letter of application notes under *"scope of application"* the reason for its inclusion as being to *"update the TRAJENTA product information with the final 2-year clinical trial results from Study 1218.20 which contains the prospectively adjudicated CV events safety results"*.

This was a multicentre, international comparator controlled study of linagliptin 5 mg by comparison with glimepiride as add-on treatment to metformin. The evaluation noted that although the sponsor's predefined criteria for noninferiority between the two treatments were met, these were superseded by the test for superiority which showed that glimepiride added to metformin was superior to linagliptin added to metformin, with a between-treatment difference in HbA1c after 52 weeks of double-blind therapy of 0.22 (0.13-0.31)% ($p<0.0001$). A higher proportion of linagliptin subjects (16.3%) than glimepiride subjects (12.1%) required rescue treatment. From the existing PI, it is noted that the incidence of hypoglycaemia in the linagliptin group was significantly lower (5.3%) than that in the glimepiride group (30.3%). Additionally, linagliptin treated patients lost on average 1.02 kg in weight from baseline with glimepiride group gained an average of 1.46 kg.

The report of this study included in the present submission includes the final 104 week data. These final results do not alter any of the findings outlined in the previous paragraph and all that has been changed in the proposed draft PI is to substitute the 104 week figures for the 52 week figures; the quoted HbA1c reduction from baseline remains at 0.4% for linagliptin and 0.6% for glimepiride; the differential in the proportions of subject experiencing hypoglycaemia remains, at 7.5% for linagliptin compared with 36.1% for glimepiride, and there is a mean weight loss of 1.39 kg for linagliptin by comparison with a weight gain of 1.29 kg for glimepiride.

The between-treatment difference in HbA1c, after 104 weeks of double-blind therapy, was now 0.20 (97.5 CI: 0.094, 0.299)% ($p<0.0001$ for superiority in favour of glimepiride). The conclusions of the previous evaluator, as noted above, are therefore sustained in relation to the 104 week data.

With regard to the stated purpose of the inclusion of this study, reference is made to the paragraph reproduced below from page 3 of the sponsor's letter of application:

"*As per Boehringer Ingelheim's pre-ACPM response dated 9 September 2011 pertaining to the original registration application for TRAJENTA [information redacted], we hereby provide the final 2-year results from Study 1218.20 [U11- 1485-02]. This study contains the prospectively adjudicated cardiovascular events safety results, which corroborate the interim (1-year) results, showing non-inferiority of linagliptin versus glimepiride in regard to the change in HbA1c from baseline (based on the pre-defined noninferiority margin of 0.35%). These results confirm that linagliptin was efficacious, well tolerated, and safe over the course of this 104-week study. A proposed update to the clinical trials section of the Product Information based on the final 2-year results from Study 1218.20 has been included in this submission.*"

This statement does not make sense. It is not the safety results which corroborate noninferiority of linagliptin, it is the efficacy results and in any case, as described above, these demonstrated superiority of glimepiride in addition to (and superseding) noninferiority of linagliptin. The update to the clinical trials section of the PI at 1.3.1 has been made and relates to efficacy, not safety. The evaluator was unaware of the context of the pre-ACPM response quoted, but the sponsor is probably referring to an adjudication of cardiac and cerebrovascular events which is

reported in the 104 week report, and is included in the product development rationale statement of the sponsor's Clinical Overview. The adjudicated analysis shows an overall lower incidence of such events in the linagliptin group (6.4%) by comparison with the glimepiride group (9.5%). These and other relevant data are discussed below in the section on cardiovascular safety.

As a study of add-on therapy, 1218.20 is not relevant to this evaluation in terms of its consideration of the proposed changes of indication for monotherapy and use with insulin. However, it validates the proposed changes to the clinical trials section of the draft PI, and has relevance to the hierarchy of drug usage discussed below in relation to the monotherapy indication.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The sponsor's Summary of Clinical Efficacy (SCE) is divided into two parts. The first, seemingly written for the application in the EU where monotherapy is already approved, summarises the evidence in relation to use with insulin. For this purpose, it defines three sets of subjects denoted EFF-1, EFF-2, and EFF-3. EFF-1 consists of the full population of Study 1218.36, all of whom were receiving insulin prior to the trial in which they were randomised to linagliptin or placebo. EFF-2 is a subset of the chronically renally impaired population of Study 1218.43; those who were receiving insulin prior to the trial. EFF-3 is a combination of EFF-1 with a subset of insulin treated patients from Study 1218.63, in which all subjects were aged >70. The numbers of subjects included in these various groupings is shown below (Table 10).

Table 10. Number of subjects included

Short-hand	Study	Patients treated in study, N	Patients included in efficacy grouping, N (%) [1]			
			Treated		FAS	
			Total, N (%)	Lina, N (%)	Total, N (%)	Lina, N (%)
EFF-1	1218.36	1261	1261 (100.0)	631 (50.0)	1235 (97.9)	618 (49.0)
EFF-2 [2]	1218.43	133	109 (82.0)	54 (40.6)	104 (78.2)	52 (39.1)
EFF-3 [3]	1218.36	1261	197 (15.6)	91 (7.2)	194 (15.4)	91 (7.2)
	1218.63	241	50 (20.7)	35 (14.5)	50 (20.7)	35 (14.5)
	Total	1502	247 (16.4)	126 (8.4)	244 (16.2)	126 (8.4)

1 Percentages refer to the overall number of patients treated within the respective trials.
2 Only patients from study 1218.43 who received insulin background therapy are included in this grouping.
3 Only patients from study 1218.36 who were aged at least 70 years and patients from study 1218.63 who received insulin background therapy are included in this grouping.

The three groupings thus provide respectively a general population of insulin treated T2DM subjects, a population of renally impaired T2DM subjects and a population of expanded age range, in each of which the effect of linagliptin added to insulin can be assessed.

The conclusions of the SCE in relation to EFF-1 and EFF-2 correspond with those drawn in the sections of this evaluation report in which studies 1218.36 and 1218.43 have been reviewed. With regard to EFF-3, a pooled analysis was undertaken of the results for the primary efficacy parameter in the two included studies, the results which are shown below (Table 11).

Table 11. Pooled analysis of primary efficacy parameter in the two included studies. EFF-3.

	Placebo	Linagliptin
Number of patients analysed	118	126
Baseline HbA_{1c} [%]		
Mean (SD)	8.20 (0.84)	8.19 (0.83)
Change from baseline HbA_{1c} at Week 24 [%]		
Mean (SD)	0.06 (0.78)	-0.71 (0.70)
Adjusted [1] mean (SE)	0.09 (0.08)	-0.68 (0.08)
Difference from placebo [%]		
Adjusted [1] mean (SE)		-0.77 (0.09)
95% Confidence interval		-0.95, -0.59
p-value		<0.0001

1 Model includes continuous baseline HbA_{1c}, treatment, study, and concomitant oral antidiabetic drugs

The size of the treatment effect (HbA1c reduction from baseline of 0.77%) is clinically significant, again consistent with the observation made earlier in relation to Study 1218.63 regarding maintenance of the effect of linagliptin in combination with insulin in older subjects. These data are relevant to the application in the sense that the target population of T2DM subjects, particularly those with longer duration of disease who more frequently require multiple therapies, includes a substantial and increasing proportion of patients aged over 70.

The second part of the SCE reviews the data from subsets of studies 1218.43 (defined as EFF-1) and 1218.50 (defined as EFF-2) in relation to the monotherapy indication (note that these EFF-1 and EFF-2 sets are quite different from those in the first part of the SCE). The subset of Study 1218.43 comprising EFF-1 consists of all those taking insulin, 104 in total. It is difficult to see how this particular subset can support an argument for use of linagliptin as monotherapy, which by definition would exclude the use of insulin. Attention has already been drawn to the relative lack of relevance of Study 1218.43 to the monotherapy indication, particularly now that it is confined to metformin-ineligible subjects, which includes the renally impaired population.

Notwithstanding the above comments, the overall conclusions of the SCE are not in conflict with the findings of this evaluation report.

6.2. Evaluator's conclusions on clinical efficacy

For use with insulin

Efficacy of linagliptin for T2DM is supported by Study 1218.36. With regard to this being a single pivotal study, it should be noted with respect to the relevant guideline[2] that this finding was statistically robust, with a clinically significant treatment effect, measured as change in HbA1c, of 0.62%. Although presented as a 24 week interim report, the submission contained sufficient data for the full 52 week duration of the study to conclude that the treatment response was enduring for that period. Efficacy with or without metformin and in the presence or absence of moderate renal insufficiency was also shown. Importantly, this was a study of adding linagliptin to insulin therapy, rather than vice versa and is therefore relevant to the most likely sequence of clinical use, as discussed below. Efficacy for this indication, with unimpaired treatment effects on HbA1c in the range 0.64-0.73%, is further supported in the population of renally impaired T2DM patients by Study 1218.43 and by Study 1218.63 in patients in the age groups over 70 and over 75. Study 1218.63 also shows that efficacy of linagliptin is maintained when added to insulin when metformin and sulphonylurea are both already being given.

[2] EMEA points to consider on application with one pivotal study, CPMP/EWP/2330/99, 31 May 2001

For use as monotherapy

Newly submitted evidence of efficacy of linagliptin for T2DM is restricted to the long-term extension (total 52 weeks) of Study 1218.50 carried out on patients ineligible for metformin due to intolerance or contraindication. The previously evaluated finding of efficacy as monotherapy in this setting, with a HbA1c treatment margin of 0.57% is confirmed, along with observational evidence that the response is maintained at 52 weeks. This observational evidence also leaves open the question of whether the size of this treatment response might be less than that obtained with a sulphonylurea (glimepiride) used as active comparator in the study. Study 1218.40 did not provide new evidence of efficacy as monotherapy, although the subset of its subjects who were recruited from Study 1218.16 did demonstrate evidence of such efficacy when that study was originally evaluated.

This evaluation does not concur with the sponsor's proposal that the final results of Study 1218.43 provide supportive evidence for use as monotherapy. However, it is felt that *use as monotherapy in patients in whom metformin is contraindicated or not tolerated* is adequately supported by the data evaluated in the original registration submission along with the findings in the final report of Study 1218.50.

7. Clinical safety

In this section, safety data is reviewed from those studies which are newly submitted in this submission, that is, 1218.36, 1218.63, and the long-term extension of 1218.50. Safety data from the remaining included studies have been covered in the relevant sections of the CERs in which they were evaluated as described above.

The sponsor's Summary of Clinical Safety (SCS) is a comprehensive document which, in addition to reviewing the safety data from the studies included in the submission, includes an updated version of the safety database for linagliptin, based on 22 studies. For this purpose, it has formed 6 groupings each containing studies of similar design, as follows:

- SAF-1: all studies in patients with T2DM
- SAF-2: placebo-controlled studies with linagliptin 5 mg
- SAF-3: placebo-controlled studies with insulin background (1218.36, 1218.43 subset, 1218.63)
- SAF-4: pivotal study with basal insulin (1218.36)
- SAF-5: patients with severe renal impairment (1218.43)
- SAF-6: elderly patients (1218.63)

Relevant to this report are groups SAF-3, 4, 5 and 6. Exposure data for these groups are reproduced below. Overall exposure and AE frequency for the entire database (SAF-1) was summarised in the SCS.

The SCS does not include a specific review of the data resubmitted for the monotherapy indication. Those studies are included in SAF-1 and SAF-2.

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy Study 1218.36

In this pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were assessed by patients being instructed to report any untoward occurrence to study personnel. All such reports were to be documented with specific questioning according to the study protocol, from the commencement of the study until the completion of 7 days following the last intake of study medication.
- AEs of particular interest were defined according to experience with other DPP-4 inhibitors and relevant regulatory recommendations and included hypersensitivity reactions, renal AEs, increased liver enzymes, cutaneous skin reactions, and pancreatitis.
- Laboratory tests, including routine haematology, general chemistry including liver function, and urinalysis, were performed on visits specified by the protocol at the central laboratory for the study.
- Hypoglycaemic episodes were specifically required to be documented. The criteria for various grades of hypoglycaemia were described in the study report.
- Physical examination, vital signs and 12-lead electrocardiogram (ECG).

Prespecified serious events were reviewed at regular intervals by an independent external Clinical Event Committee.

7.1.2. Pivotal studies that assessed safety as a primary outcome

No studies of this type submitted.

7.1.3. Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy studies provided safety data, as follows:

- Study 1218.63 provided data on 162 patients treated with linagliptin and 79 with placebo.
- Study 1218.50 provided data on 137 patients treated in Part 2 of the study with linagliptin and 64 with the active comparator glimepiride (safety data for Part 1 was reviewed in the previous CER).

7.2. Pivotal studies that assessed safety as a primary outcome

No studies of this type submitted.

7.3. Patient exposure

Patient numbers and exposure to placebo and linagliptin for the study groupings reviewed in this report, as described above, are shown below (Table 12).

Table 12. Patient exposure

	SAF-3		SAF-4	
	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
Number of patients, N (%)	700 (100.0)	720 (100.0)	630 (100.0)	631 (100.0)
Exposure categories, N (%)				
≥24 weeks	631 (90.1)	664 (92.2)	580 (92.1)	598 (94.8)
≥52 weeks	218 (31.1)	229 (31.8)	186 (29.5)	197 (31.2)
Duration of treatment exposure [days]				
Mean (±SD)	292 (116.5)	297 (111.8)	295 (114.5)	303 (110.0)
Median (minimum, maximum)	295 (1, 531)	298 (3, 531)	292 (4, 531)	304 (3, 531)
Overall patient years	559.0	585.1	508.8	523.6

	SAF-5		SAF-6	
	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
Number of patients, N (%)	55 (100.0)	54 (100.0)	121 (100.0)	126 (100.0)
Exposure categories, N (%)				
≥24 weeks	42 (76.4)	47 (87.0)	103 (85.1)	109 (86.5)
≥52 weeks	32 (58.2)	32 (59.3)	34 (28.1)	26 (20.6)
≥78 weeks	0	0	0	0
≥102 weeks	0	0	0	0
Duration of treatment exposure [days]				
Mean (±SD)	290 (132.6)	315 (103.9)	283 (122.0)	265 (107.5)
Median (minimum, maximum)	364 (1, 384)	364 (29, 396)	293 (4, 527)	244 (11, 531)
Overall patient years	43.6	46.6	93.8	91.3

Note that exposure data for SAF-5 (Study 1218.43) will have been included in the previous evaluation.

7.4. Adverse events

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

7.4.1.1. Pivotal study

The overall incidence of AE was similar in the two treatment groups (72.5% placebo, 71.0% linagliptin). Likewise, AEs regarded as severe (SAE) were reported for 58 placebo patients (9.2%) and 15 (2.4%) linagliptin patients. AEs predefined to be of special interest, as described above, and requiring description by the investigator, were reported for 12 patients (1.9%) in each treatment group; nevertheless, there was an apparent imbalance for hypersensitivity reactions (all urticaria), which occurred in 1 placebo patient and 4 linagliptin patients; and of pancreatitis which occurred in 1 placebo and 3 linagliptin patients. 2 of these 3 cases were classified as chronic pancreatitis, which may not have started during the study period.

Particular note was taken of AEs related to the potential development of cancer (System Organ Class (SOC) benign, malignant and unspecified neoplasms, including cysts and polyps). The overall incidence of this SOC was similar in the placebo and linagliptin groups (1.4% and 1.6% respectively) but there was an imbalance with respect to the development of thyroid neoplasms (4 linagliptin patients, none on placebo). These are described as being not serious and not requiring treatment, so it is presumed that they were benign thyroid nodules.

Hypoglycaemia was defined as an AE of interest but is regarded by this evaluator as a treatment outcome and is discussed above in the study report.

7.4.1.2. Other studies

In Study 1218.50, reports of AE occurred in 62.5% of glimepiride and 59.9% of linagliptin patients. Interpretation of this data with regard to linagliptin is rendered difficult by the active

controlled nature of the study. Because of this, comment will not be made about findings from this study in the following sections except in any case of obvious imbalances. There was no evidence of any significant incidence of protocol specified AEs. A single case of hypersensitivity reaction occurred in each treatment group.

In Study 1218.63, the proportion of patients reporting an AE was identical (75.9%) in the placebo and linagliptin groups. With regard to prespecified protocol defined AE of special interest, 4 cases were identified in patients receiving linagliptin. Two of these were deterioration in renal function, each of which resolved spontaneously without ceasing the medication. The other 2 were dermatological problems, one with eczema and the other with moderate contact dermatitis which may have been drug-related in relation to hypersensitivity. There were no cases of pancreatitis. Nasopharyngitis was evenly distributed between the linagliptin and placebo groups.

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

7.4.2.1. Pivotal study

AE considered by the investigator to be treatment-related were reported for 114 placebo patients (18.1%) and 100 linagliptin patients (15.8%).

7.4.2.2. Other studies

In Study 1218.63, AEs regard as drug-related were reported in 34 (21%) linagliptin by comparison with 11 (13.9%) placebo patients. There was an obvious imbalance in hypoglycaemic events which occurred more commonly (14.8% versus 8.9%) in the linagliptin group, attributable to the improved control in this group and concomitant insulin use. Otherwise there was no significant imbalance between the two groups.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal study

During the period of randomised treatment, one patient in each study group died, and a further patient who had been on linagliptin died during the post treatment period.

Comment: Although none of these patients underwent autopsy, the causes of death presumed from the study narratives appear unlikely to have been related to study medication. Furthermore, these 3 deaths represent a mortality rate during the period of study treatment of approximately 0.5 per 100 patient-years, which is in the lower part of the range 0.25-8.4 described in a recent survey of clinical trials of this nature.[3]

7.4.3.2. Other studies

In Study 1218.50 part 2, 1 patient who had been on linagliptin died at home of presumed myocardial infarction three weeks after stopping the study drug because of a previous non-fatal infarct. Five other SAE are described, 2 of which occurred on linagliptin, one being an unplanned pregnancy which had a catastrophic outcome with ruptured uterus and foetal death, obviously not related to the study treatment.

Somewhat surprisingly given the age group involved, no deaths occurred during Study 1218.63. The incidence of SAE was similar between the treatment groups and none appears likely to have been medication related.

[3] Barkoudah E, Skali H, Uno H, Solomon SD, Pfeffer MA. (2012). Mortality rates in trials of subjects with type 2 diabetes. *J Am Heart Assoc* 1: 8-15

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal study

This situation arose for 21 patients (3.3%) in the placebo group and 15 (2.4%) on linagliptin. Perusal of the specific causes reveals no particularly unusual events or imbalance between the two treatment groups, except that there were 3 discontinuations in the placebo group due to hyperglycaemia, which is reflective of the overall outcome of the study.

7.4.4.2. Other studies

In Study 1218.50 Part 2, AEs leading to discontinuation occurred in 5 linagliptin and 1 glimepiride patients. In none of the former do the causes seem unusual or specifically treatment-related.

In Study 1218.63, 8 (4.9%) of linagliptin by comparison with 1 (1.3%) placebo patients discontinued treatment after an AE. The reasons for this apparent imbalance have already been discussed above in the study report and appear unrelated to the study drug.

7.4.5. Laboratory tests

For pivotal Study 1218.36, the numbers of patients in the placebo and linagliptin groups with possibly clinical significant laboratory abnormalities (PCSA) was included.

7.4.6. Liver function

7.4.6.1. Pivotal study

The numbers of patients with PCSA of liver function tests were small, with no trend evident between the placebo and linagliptin groups. A single patient in the placebo group developed abnormalities potentially fulfilling Hy's law, a set of criteria designed to alert the possibility of significant drug induced liver injury.[4] The patient was diagnosed with hepatitis B.

7.4.6.2. Other studies

In Study 1218.63, there were 5 (3.2%) linagliptin by comparison with 2 (2.6%) placebo patients with possibly significant increases in GGT but no PCSA of other liver function tests were reported. There were no Hy's law cases.

7.4.7. Kidney function

7.4.7.1. Pivotal study

Given that a proportion of the population of this study had impaired renal function at entry, there were a significant number of laboratory abnormalities in this category. However, no imbalance was seen in this respect between the two study groups or between the numbers of subjects in each group whose level of renal impairment deteriorated during the study, as shown in the study report. Likewise there was no imbalance with regard to albuminuria.

7.4.7.2. Other studies

In Study 1218.63, PCSA of increased creatinine occurred in 12 (7.6%) linagliptin compared with three (3.9%) placebo patients. This may be of some significance in relation to the observation of 2 clinical AE of deterioration in renal function as described above. It should be noted that the majority of the participants in this study of older T2DM patients had some degree of renal impairment at baseline.

[4]Drug induced liver disease. Zimmerman HJ. In: Hepatotoxicity, the Adverse Effects of Drugs and Other Chemicals on the Liver, 1st edition pp 351-3 (1978)

7.4.8. Other clinical chemistry

7.4.8.1. Pivotal study

No significant imbalance is noted between placebo and linagliptin.

7.4.8.2. Other studies

No imbalances of significance were noted between the linagliptin and placebo groups in Study 1218.63.

7.4.9. Haematology

7.4.9.1. Pivotal study

Imbalances of PCSA described as minor were noted between the study groups for the proportions of patients with decreased haemoglobin (3.1% placebo; 6.4% linagliptin), red blood cell count (1.3% placebo; 2.4% linagliptin), and white blood cell count (1.0% placebo; 6.4% linagliptin). There were however no reported AEs of anaemia or neutropenia and inspection of the statistical summary for haematology data shows that the mean values for all of the above parameters were close to identical between the placebo and linagliptin groups, with no indication in the minimum or variance parameters that there was a significant subpopulation of low values.

7.4.9.2. Other studies

In Study 1218.63 there were no clinically relevant abnormalities.

7.4.10. Electrocardiograph

7.4.10.1. Pivotal study

ECG was performed at regular intervals during the study but the study report contains no description of AEs or imbalance between AE with regard to the findings.

7.4.10.2. Other studies

Reports of abnormalities on routine ECG monitoring were not found.

7.4.11. Vital signs

In all three studies reviewed here, vital signs were measured at each visit but did not vary between the treatment groups, or over time.

7.4.12. Cardiovascular safety

Under the heading "*Post market*" the sponsor's submission contains the report dated 19 December 2011 on a pooled safety analysis of cardiovascular risk drawn from all Phase III studies then available in the sponsor's database for linagliptin. Included subjects totalled 7907, comprising 4893 on linagliptin 5 mg daily or 2.5 mg twice daily, 2081 on placebo and 937 on active control with either voglibose or glimepiride.

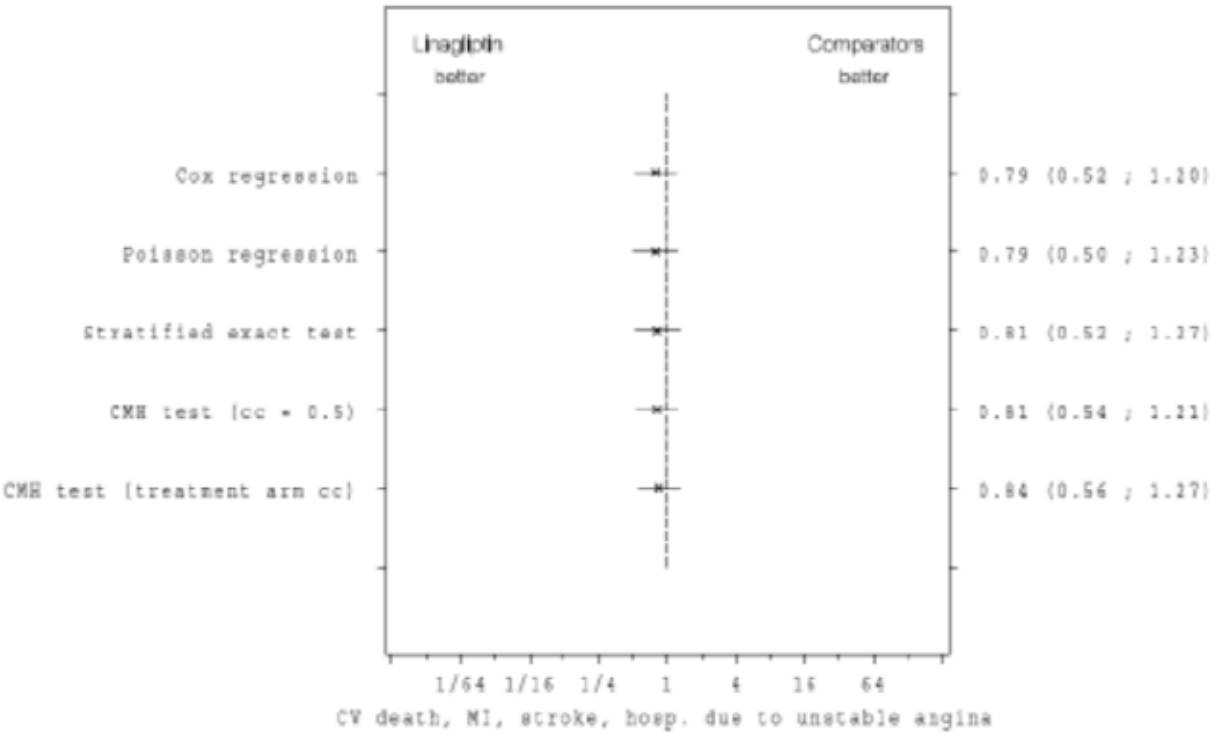
The analysis employed individual patient data from 13 trials.

An independent CEC adjudicated major cardiovascular events occurring during the studies, including cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, unstable angina pectoris with and without hospitalisation, stable angina pectoris and transient cerebral ischaemic attacks. These collectively represent clinical consequences of coronary and cerebrovascular disease. The primary composite endpoint for the meta-analysis comprised the more severe events of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or unstable angina pectoris with hospitalisation.

For this primary endpoint, 44 events were observed in the linagliptin group and 45 in the combined placebo/active control comparator group, yielding incident event rates of 12.0 and

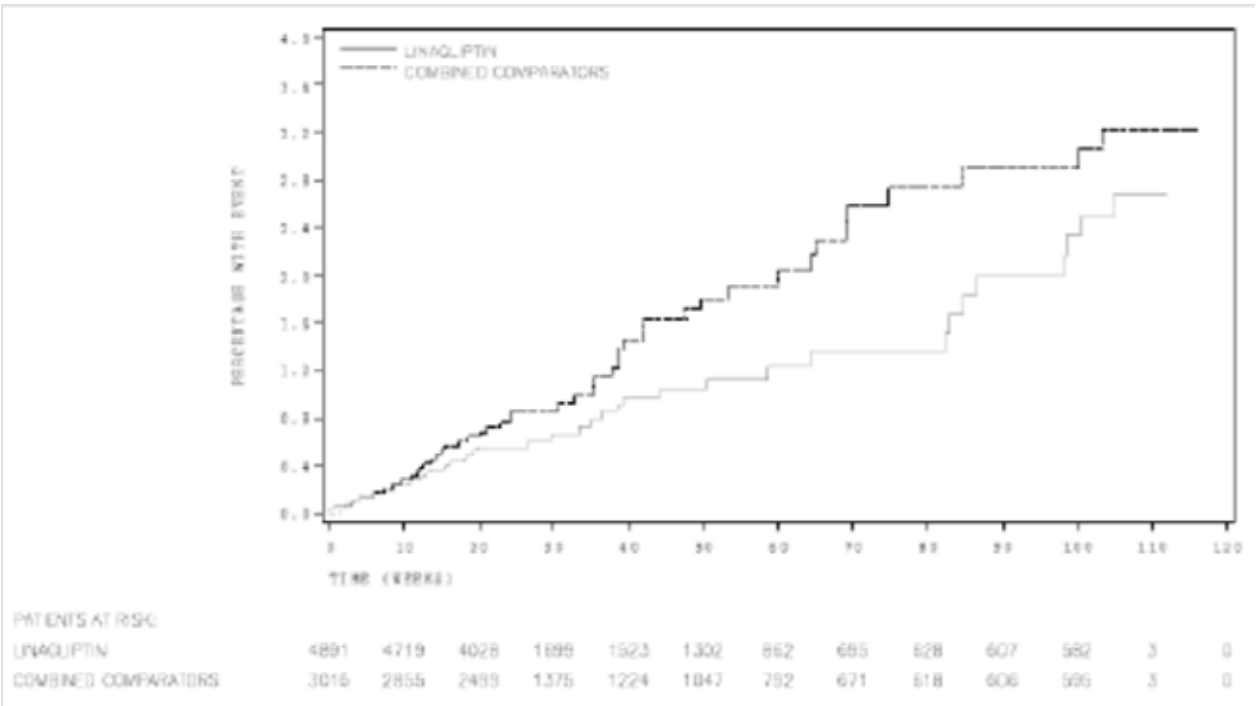
16.9 per 1000 years of exposure respectively. Using a variety of statistical methods, cardiovascular risk by comparison between these two groups were calculated with 95% CI, and a Forrest plot of these data is shown below (Figure 7).

Figure 7. Forrest plot of Cardiovascular risk.



The reduction in risk with linagliptin does not achieve significance but some trend towards the emergence of a difference over time is shown by the following Kaplan-Meier plot of the data (Figure 8).

Figure 8. Kaplan Meier plot



A number of secondary endpoints were analysed, including an FDA defined criterion of major adverse cardiovascular events (MACE). The individual risk event categories listed earlier were also analysed as tertiary endpoints. Of these, events of stroke and transient cerebral ischaemic attack were observed by Cox regression to be significantly lower for linagliptin compared with the combined comparators.

The conclusion of the pooled analysis was that treatment with linagliptin, with or without background therapy, does not increase cardiovascular risk compared with a combined comparator group (placebo, glimepiride and voglibose)

Reference has already been made in the report on active controlled Study 1218.20 to an adjudicated analysis which showed an overall lower incidence of cardiovascular events (6.4%) in the linagliptin/metformin group of 776 subjects by comparison with 9.5% in the glimepiride group of 775 subjects. A post-hoc analysis of the difference in incidence between the groups of cardiovascular events confirmed by the CEC showed moderate levels of statistical significance for some of the groupings as shown below (Table 13).

Table 13. Post-hoc analysis of the incidence of cardiovascular events.

	Linagliptin		Glimepiride		p-value[1,2]	Relative risk[2]	95% Confidence interval[4]
	N	(%)	N	(%)			
Combined cardiovascular events[3]	12	(1.6)	26	(3.4)	0.0213	0.46	(0.23, 0.91)
Individual events							
CV death (including fatal stroke)	2	(0.3)	2	(0.3)	0.9990	1.00	(0.14, 7.07)
Non-fatal MI	6	(0.8)	10	(1.3)	0.3136	0.60	(0.22, 1.64)
Non-fatal stroke	3	(0.4)	11	(1.4)	0.0315	0.27	(0.08, 0.97)
Stable angina	11	(1.4)	12	(1.6)	0.8312	0.92	(0.41, 2.06)
Unstable angina							
with hospitalisation	3	(0.4)	3	(0.4)	0.9987	1.00	(0.20, 4.93)
without hospitalisation	0	(0.0)	0	(0.0)	0.9995	1.00	(0.02, 50.27)
Transient ischaemic attack	1	(0.1)	5	(0.7)	0.1015	0.20	(0.02, 1.71)
Total mortality	4	(0.5)	4	(0.5)	0.9985	1.00	(0.25, 3.98)

All events were independently adjudicated by CEC and analysed as part of the planned cardiovascular meta-analysis on the project level

[1] From chi-squared test

[2] With continuity correction of 0.5

[3] Including cardiovascular death, myocardial infarction, stroke, and hospitalisation due to unstable angina

[4] 2-sided 95% confidence interval on a logarithmic scale

Comment: If these data are taken as supporting the possibility of linagliptin having a beneficial effect on cardiovascular outcome by comparison with glimepiride, it would have to be assumed that such an effect was not simply dependent upon the effect on glycaemic control, as in this trial the effect on glycaemic control was superior for glimepiride added to metformin by comparison with linagliptin added to metformin. The absence of a comparison with placebo also renders interpretation difficult.

7.4.12.1. Conclusion on cardiovascular safety

Both sets of data described above provide reassurance that linagliptin is not associated with an increased risk of cardiovascular events, as has been suggested to occur with some oral hypoglycaemic agents. A major goal of all treatment for T2DM is to reduce cardiovascular risk, this being the major cause of morbidity and premature mortality in people with diabetes. The data support the possibility that this might be demonstrated for linagliptin although there should become some caution about the possibility of a type 1 error when noting isolated events of significant difference amongst multiple endpoints, as in this case. The overall trend of the data, nevertheless, is towards linagliptin having a beneficial effect on cardiovascular risk. Available data on this subject should be kept up-to-date in the PI.

7.5. Postmarketing experience

The data on cardiovascular safety referred to in the previous section was the only post marketing information contained in the submission.

7.6. Safety issues with the potential for major regulatory impact

No new issues were identified in this evaluation. Adverse effects previously identified as potential risks for this drug class (such as hypersensitivity reactions and pancreatitis) were not observed to be of any greater incidence in the data reviewed for this submission.

7.7. Other safety issues

7.7.1. Safety in special populations

The study populations in the submission contained a significant proportion of subjects in older age groups and with impaired renal function. No specific safety issues were identified for these populations, although it should be observed that in each case the number of subjects exposed to linagliptin was relatively small: 54 in the case of the renally impaired population SAF-5, and 126 for the elderly population SAF-6 (Table 12).

7.8. Evaluator's overall conclusions on clinical safety

The profile of adverse events by comparison with placebo shows no pattern to suggest any newly emergent safety concern regarding linagliptin. There was a minor incidence of specified adverse effects (hypersensitivity, pancreatitis) which have been previously identified as being associated with this drug. Linagliptin shows a low incidence of hypoglycaemia, particularly by comparison with a sulphonylurea which is a therapeutic alternative choice in the proposed usage. The findings on cardiovascular risk do not suggest any adverse effect of linagliptin in this respect and invite continuing analysis for the possibility of a beneficial effect.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of linagliptin in the proposed usage are:

- Improved diabetes control as measured by HbA1c reduction.
- Availability of a therapeutic alternative for patients unable to take metformin, whether because of intolerance or contraindication due to impairment of renal function.
- Consequent likelihood (yet to be proven for this class of drugs) of reduced risk of diabetes complications.
- Reduced risk of hypoglycaemia and weight gain by comparison with most likely therapeutic alternative (sulphonylurea), at least in the monotherapy usage.
- In the insulin usage, reduction in insulin dosage; although whether that is beneficial per se is arguable.

8.2. First round assessment of risks

The risks of linagliptin in the proposed usage are:

- A low level of risk of described class specific side-effects including hypersensitivity reactions and pancreatitis.
- Safety of use in patients aged 70 or above, and in those with impaired renal function, is at this stage dependent on the observation of relatively limited exposure.
- Potential (and inestimable) future risk of presently unforeseen side-effects for this relatively new drug by comparison with therapeutic alternatives with long safety records (for example, insulin, sulphonylureas).

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of linagliptin in both aspects of the proposed indication was considered favourable, assuming that the proposed monotherapy usage is adjusted to include only patients ineligible for metformin.

9. First round recommendation regarding authorisation

As mentioned above, clinical practice regarding the positioning of recently introduced blood glucose lowering agents, including DPP-4 inhibitors, is in a state of evolution. Currently, three DPP-4 inhibitors in addition to linagliptin (sitagliptin, saxagliptin and vildagliptin) are registered for use in Australia with differing approved indications. All three are approved as add-on therapy to metformin, a sulphonylurea or a thiazolidinedione. Sitagliptin is also approved as monotherapy when metformin cannot be used. Sitagliptin and saxagliptin are each approved for initial combination therapy with metformin in specific clinical circumstances (high initial HbA1c and poor prospects of response to monotherapy). Most recently (TGA approval 19 September 2012), a limited indication for use with insulin (basal and pre-mixed insulin only, with or without metformin) has been approved for saxagliptin. These differences, which may be confusing to the prescriber, appear to be related not so much to differences in the properties of the various drugs as to variations in the trial design and types of evidence presented in submissions for registration.

Given the evaluation and regulatory process involved, it can be concluded from the above discussion that there is an evidence base and a positive benefit/risk balance supporting the use of DPP-4 inhibitors as a class in the following therapeutic situations: monotherapy when metformin cannot be used, add-on therapy to the other OHA classes mentioned, initial combination with metformin in defined clinical circumstances, and use with insulin. Consideration of any of these indications for other members of the class such as linagliptin is therefore reasonable provided there is adequate supporting evidence. In this particular application, use as monotherapy and use with insulin are the additional indications requested and these are discussed separately below.

9.1. Use as monotherapy

Consideration of this aspect of the application was initially influenced by uncertainty as to the sponsor's intentions. Although the letter of application includes in the proposed new indication the use "as monotherapy", without qualification, it goes on, on the following page, to indicate that the company now accepts that monotherapy should be restricted to metformin-ineligible patients, and this intention is clearly supported by the summary in the sponsor's Clinical Overview, as discussed above. In view of this, it will be assumed for the purpose of this evaluation report that the application is in fact for monotherapy in metformin-ineligible patients. The sponsor's letter of application and the sponsor's Clinical Overview request consideration of the resubmission for monotherapy on the basis of the final results of Studies 1218.43 and 1218.50 *"together with the previously submitted data"*. The pivotal study for the

unrestricted monotherapy application in the original submission was Study 1218.16 which was evaluated in the CER for the submission but not included amongst the data for the present submission. The study was carried out on treatment-naive patients and demonstrated superiority to placebo with a treatment difference in HbA1c of 0.69%. However, the evaluator did not recommend first-line treatment based on this data on the basis that other submitted data showed linagliptin to be inferior to sulphonylurea in this situation and that there was no data comparing it with metformin as initial monotherapy. The evaluator recommended that an alternative indication suitable for approval might be *"…. as monotherapy (where both metformin and sulphonylureas are either ineffective or contraindicated)….".* Apart from the reference to sulphonylureas, this is effectively what is now being requested.

The findings of Studies 1218.43 and 1218.50, which support efficacy in monotherapy for metformin-ineligible patients, together with the benefit-risk balance for use in that situation, have been reviewed above.

9.1.1.1. Positioning linagliptin relative to sulphonylureas

The recommendation of the previous evaluator that monotherapy only be considered where both metformin and sulphonylureas are either ineffective or contraindicated cannot be lightly dismissed. Sulphonylureas were the first class of oral hypoglycaemic agent to be used and apart from the important possibility of causing hypoglycaemia, have a well-established safety as well as efficacy profile. Prior to the introduction of new classes of oral agents including thiazolidinediones and DPP-4 inhibitors, most treatment algorithms placed sulphonylureas as first choice for add-on treatment to metformin, or even first-line treatment for the small proportion of non-obese T2DM patients. The fact that they are much less costly might also be a factor in circumstances not relevant to this evaluation report.

No evidence has been produced in this submission, or to the evaluator's knowledge in any of the related submissions for linagliptin, that when used alone it has efficacy superior to that of sulphonylureas. If anything, the reverse may be the case; as discussed above, in a long-term double-blind controlled study greater HbA1c reduction was seen with glimepiride than with linagliptin. This was in the context of add-on treatment to metformin but given the differing and complementary actions of the three drugs, it is as likely as not that the same effect would be observed in the absence of metformin. Phase 2 Study 1218.6, reviewed in the CER of the original submission for registration showed in drug naive T2DM patients a HbA1c reduction at 12 weeks of 0.73% in subjects randomised to 5 mg double-blind linagliptin by comparison with 0.90% with open label glimepiride; and in a similar study with open label metformin as the active comparator (1218.5) the HbA1c reduction was 0.46% for 5 mg linagliptin by comparison with 0.85% for metformin.

On the basis of efficacy alone, therefore, it is difficult to recommend linagliptin (or possibly other DPP-4 inhibitors) as monotherapy in preference to sulphonylureas in the absence of intolerance or contraindication to the latter, something which occurs much less frequently than with metformin. However, there are safety risks to be considered, particularly the much greater incidence of hypoglycaemia with sulphonylureas. The nature of the risk/benefit equation will vary between individuals, either due to their personal history of hypoglycaemia, or occupation (for example, heavy transport driver) or other medical conditions (such as epilepsy). In view of this, it is felt that the choice between linagliptin and sulphonylurea is best left to the treating clinician, taking account of the patient's circumstances. The situation regarding the choice between linagliptin and metformin is different, as the contraindication and intolerance issues are more clearly defined and in their absence, there is no reason to favour linagliptin.

In summary, it *is recommended that use as monotherapy in patients ineligible for metformin be approved*, without qualification with regard to sulphonylurea use. With regard to clarity for the prescriber, it may be of some benefit that this is equivalent, as discussed above, to the

conditions for the only other DPP-4 inhibitor currently approved for use as monotherapy in Australia.

9.2. Use with insulin

In the introduction to the summary of the submission in the sponsor's Clinical Overview, it is stated that "With the present submission, Boehringer Ingelheim is applying for the use of linagliptin as combination therapy with insulin in adult patients with T2DM when insulin with or without oral antidiabetic drugs (metformin, pioglitazone, sulphonylurea) does not provide adequate glycaemic control". It is thus defined that the target population for this combination therapy includes patients whose treatment includes various combinations of metformin, pioglitazone, and sulphonylureas. The inclusion of all of these drug classes in the proposed indication once linagliptin is added, however, demands evidence of efficacy with regard to each of them.

With regard to **metformin**, pivotal Study 1218.36 provides adequate evidence that linagliptin is effective when added to insulin whether in the presence of or in the absence of metformin. It would in any case be therapeutically irrational to prefer linagliptin to metformin as an add-on therapy to insulin, unless metformin was contraindicated or not tolerated.

The submitted evidence does not support the inclusion of **pioglitazone** in the therapeutic equation proposed. The only relevant study was 1218.36, which included small subsets of subjects taking pioglitazone (1% of study population) or pioglitazone and metformin (7.4% of study population) as well as insulin. Analysis of the primary efficacy parameter, HbA1c change from baseline, showed that the treatment margin of linagliptin over placebo was unchanged and remained significant in the pioglitazone + metformin subset, by comparison with the majority subset taking metformin alone with insulin (see Table 4). The pioglitazone therapy was pre-existing and not determined by randomisation. The data does not exclude the possibility of additional therapeutic benefit from pioglitazone in combination with linagliptin, metformin and insulin but neither does it prove it. The subset of subjects taking pioglitazone alone with insulin was too small to allow any conclusions about the benefit of linagliptin in that combination. Furthermore, there is no existing approval for use of linagliptin in any combination with pioglitazone, and to allow its use specifically in this situation together with insulin with or without metformin would require much stronger evidence than is found in this study.

The situation with regard to **sulphonylurea** is somewhat similar. This class of drug was not used in pivotal Study 1218.36 and no sub-analyses by class of background therapy were performed in Study 1218.43. Some evidence of efficacy for the linagliptin + sulphonylurea + metformin + insulin combination is seen in Study 1218.63, in which the group so treated achieve the greatest effect size in terms of HbA1c change but again there is no randomisation to the sulphonylurea component or statistical analysis by comparison with the linagliptin + metformin combination with insulin. The situation is nevertheless slightly different in that there is evaluated evidence supporting an existing indication for the triple linagliptin + sulphonylurea + metformin combination, or linagliptin + sulphonylurea, without insulin.

It is therefore recommended that on the basis of the evidence submitted, *use of linagliptin be approved as add-on treatment to insulin with or without metformin*. This evaluator would have no objection to this being extended to use as *add-on to insulin with or without metformin and/or sulphonylurea,* although the evidence is marginal. *Use with pioglitazone in any combination was not supported.*

9.3. Proposed indication

In line with the above comments, it was recommended that the proposed indication be altered to the following:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when metformin is not tolerated or contraindicated, or as add on to metformin, sulphonylureas or metformin plus sulphonylureas, or to insulin (with or without metformin* ***and/or sulphonylureas****).*

The phrase "and/or sulphonylureas" in bold should be removed if it is felt inappropriate to include it on the basis of marginal evidence.

The above could be slightly simplified and shortened, if thought appropriate, as follows:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when metformin is not tolerated or contraindicated, or as add on to metformin and/or sulphonylureas, or to insulin (with or without metformin and/or sulphonylureas). This would assume that the phrase metformin and/or sulphonylureas can legitimately be taken to include the combination of the two drugs/classes.*

If the recommendation of this report to approve monotherapy without qualification as to sulphonylurea use is not accepted, the words *"metformin and sulphonylureas are"* could be substituted for *"metformin is"* in the second line of either version.

10. Clinical questions

10.1. Safety

No questions, although the comment above regarding the desirability of bringing the cardiovascular safety information in the draft PI up to date should be addressed.

11. Second round evaluation of clinical data submitted in response to questions

Not applicable.

12. Second round benefit-risk assessment

Not applicable.

13. Second round recommendation regarding authorisation

Not applicable.

14. References

1. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman R, Sherwin R, Zinman B. (2009). Medical management of hyperglycaemia in type II diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32 (1): 193.

2. EMEA points to consider on application with one pivotal study, CPMP/EWP/2330/99, 31 May 2001

3. Barkoudah E, Skali H, Uno H, Solomon SD, Pfeffer MA. (2012). Mortality rates in trials of subjects with type 2 diabetes. *J Am Heart Assoc* 1: 8-15

4. Drug induced liver disease. Zimmerman HJ. In: Hepatotoxicity, the Adverse Effects of Drugs and Other Chemicals on the Liver, 1st edition pp 351-3 (1978)

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au