Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for ERWINASE

Active ingredient: Crisantaspase

Sponsor: PPD Australia

June 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ADA	Anti-drug antibody(ies)
ADR	Adverse drug event
ALL	Acute lymphoblastic leukaemia
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
ASNase	Asparaginase
AST	Aspartate transaminase
ATIII	Anti-thrombin III
BFM	Berlin Frankfurt Munster
BSA	Body surface area
CALGB ALL	Cancer and Leukaemia Group B ALL
CCG	Children's cancer group
CMI	Consumer medicines information
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response
Crisantaspase	Erwinia asparaginase; asparaginase Erwinia chrysanthemi, ERWINASE, Erwinaze
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common Technical Criteria for Adverse Events
DFCI	Dana Farber Cancer Institute
DFS	Disease free survival
DLP	Data lock point
DI	Delayed intensification
DSMB	Data safety monitoring board
EFS	Event free survival
EMA	European Medicines Agency
FDA	Food and Drug Administration
HR	High risk
Hyper-CVAD	Hyper Cyclophosphamide Vincristine Adriamycin (doxorubicin) and Dexamethasone
IQR	Interquartile range
IM	Intramuscular
IU	International units
IV	Intravenous
LFS	Leukaemia free survival
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MTX	Methotrexate
NCE	New chemical entity

Abbreviation	Meaning
NSAA	Nadir serum asparaginase activity
NOPHO	Nordic Society of Paediatric Haematology and Oncology
OR	Odds ratio
OS	Overall survival
PBRER	Periodic benefit risk evaluation report
PD	Progressive disease
PEG ASNase	PEGL, Pegaspargase, PEG-L-asnase, pegylated asparaginase, Oncaspar
PH	Philadelphia chromosome
PI	Product information
PR	Partial response
PRAC	Pharmacovigilance risk assessment committee (of the EMA)
PSUR	Periodic safety update report
PT	Prothrombin time
PTT	Partial thromboplastin time
RER	Rapid early responders
RMP	Risk management plan
RR	Response rate
SEM	Standard error of the mean
SER	Slow early responders
SGPT	Serum glutamic pyruvic transaminase
SLR	Systematic literature review
SOC	System organ classification
SR	Standard risk
TGA	Therapeutic Goods Administration
WCC	White cell count

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	ERWINASE
Active ingredient:	Crisantaspase
Decision:	Approved
Date of decision:	6 February 2024
Date of entry onto ARTG:	14 February 2024
ARTG number:	371877
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	PPD Australia Pty Ltd, Level 5, 412 St Kilda Road, Melbourne, Australia
Dose form:	Powder for solution for injection/infusion.
Strength:	10,000 IU Cristantaspase/vial (One unit of asparaginase activity is defined as the amount of enzyme that catalyses the hydrolysis of one micromole of L-asparagine per minute at pH 8.6 and 37°C)
Container:	Glass vial
Pack size:	1 carton box of 5 vials
Approved therapeutic use for the current submission:	ERWINASE is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to pegylated asparaginase obtained from *E. coli*.
Routes of administration:	Intravenous, Intramuscular
Dosage:	25,000 International Units/m^2 administered intramuscularly or intravenously three times a week (Monday/Wednesday/Friday) for six doses. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during

pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by PPD Australia Pty Ltd (the Sponsor) to register ERWINASE (Crisantaspase) for the following proposed indication:[1]

> *Erwinase is used in combination with other chemotherapeutic agents to treat patients, principally children, with acute lymphoblastic leukaemia who have developed hypersensitivity to E. coli asparaginase or pegylated asparaginase obtained from E. coli.*

Asparaginase is an integral component of multicomponent regimens used to treat patients with ALL. *E. coli*-derived asparaginase either native or pegylated has been the initial asparaginase used for many decades. Due to hypersensitivity reactions (around 1/3 of patients) or silent inactivation (where there is an unexplained lack of activity presumed secondary to neutralising antibodies) *E. coli*-derived asparaginase may not be suitable for all patients.

The Sponsor seeks to register a substitution asparaginase, Crisantaspase, for patients who cannot continue their initial asparaginase.

The disease/condition[2,3,4]

Acute lymphoblastic leukemia (ALL) is a malignant disease of T or B lymphocytes characterised by clonal expansion of immature lymphocytes and their progenitors that leads to the replacement of normal hematopoietic cells and cells in other lymphoid organs. B cell ALL is the most common type (70% to 80%) in children and adults, with T cell ALL comprising 10% to 25% of paediatric and adult ALL.

The peak age incidence is in the paediatric age range although it can occur at any age. The prognosis is less favourable in infants aged <1 year, B-cell ALL, higher white cell count (≥50,000/mL) and in adults. Its aetiology is unknown, but it is more common in patients with Trisomy 21, neurofibromatosis type 1, Bloom syndrome and ataxia telangiectasia. Exposure to environmental chemicals and germline mutations in PAX5, ETV6, P53 and somatic mutations of ARD5B, IKZF1 and ADKN2A have been implicated.

Presentation is commonly non-specific, with a combination of constitutional symptoms such as fever, weight loss, night sweats together with symptoms related to bone marrow failure, with fatigue and dyspnoea due to anaemia, bruising due to thrombocytopenia and infections due to neutropenia. Lymphadenopathy, splenomegaly and hepatomegaly may occur. CNS involvement may be present at diagnosis and present as cranial nerve deficits or meningismus. T-cell ALL also may present with a mediastinal mass and superior vena cava obstruction.

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Terwilliger, T., Abdul-Hay, M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 7, e577 (2017). https://doi.org/10.1038/bcj.2017.53

[3] American Cancer Society, Key Statistics for Acute Lymphocytic Leukemia. Accessed October 2021 at Key Statistics for Acute Lymphocytic Leukemia (ALL) (cancer.org)

[4] Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med 2015;373:1541-1552. DOI: 10.1056/NEJMra1400972

Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Morphology, flow cytometry immunophenotyping, molecular and cytogenetic testing is performed to determine the subtype and to assist in risk stratification and treatment guidance.

The currently accepted classification of ALL is the World Health Organisation classification that divides ALL into B-lymphoblastic leukemia/lymphoma and T-lymphoblastic leukemia/lymphoma, and further subtypes according to the presence of recurrent genetic abnormalities, as follows.

B lymphoblastic leukemia/lymphoma:

- B-lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
  - B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
  - B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
  - B-lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukemia/lymphoma with hypodiploidy
  - B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
  - B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
  - Provisional: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*–like
  - Provisional: B-lymphoblastic leukemia/lymphoma with *iAMP21*

T lymphoblastic leukemia/lymphoma:

- Provisional: Early T-cell precursor lymphoblastic leukemia
- Provisional: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Acute lymphoblastic leukemia in Australia

There were 364 cases of ALL diagnosed in Australia in 2017. Of these, 56% were aged 0-19 years and 13% were aged 60-79 years. The number of cases overall was predicted to increase to 446 in 2021.

The 5-year survival rate in the Australian population with ALL has improved from 55% for all ALL patients in 1988-1992 to 73% in 2013-2017. In the latter 5-year period, the observed 5-year survival rate progressively declined with age: from 94% in children aged 0 to 9 to 80% in young adults aged 20 to 29 years and 42% in adults aged more than 60 years.

Asparaginase

Crisantaspase belongs to the same pharmacological class as asparaginase (colaspase; LEUNASE) and pegylated asparaginase (pegaspargase; ONCASPAR), first approved for similar indications in paediatric and adult patients by the TGA in 1991 and 2019, respectively. *Erwinia* L-asparaginase is an *Erwinia chrysanthemi* derived Type II asparaginase, while asparaginase in LEUNASE and ONCASPAR is derived from *E. coli*.

Asparaginase hydrolyses asparagine to aspartic acid and ammonia. Asparagine is a non-essential amino acid and is synthesised from aspartic acid and glutamine by the enzyme asparagine synthetase (ASY) in mammalian cells. Published studies have demonstrated cancer cells have a

reduced ability to synthesise asparagine and require an asparagine source for viability. Leukemia lymphoblasts also have low levels of asparagine synthetase and are dependent on exogenous asparagine. Asparaginase depletes circulating levels of plasma L- asparagine, selectively killing lymphoblasts. Childhood ALL also has low expression of asparaginase probably due to methylation of the *ASY* gene. Thus, depletion of asparagine in blood by asparaginase results in inhibition of protein synthesis, DNA synthesis and RNA synthesis of ALL cells and results in apoptosis of cancer cells. In contrast, normal cells are otherwise capable of synthesising asparagine and are therefore less affected by its rapid withdrawal during treatment with L-asparaginase.

Asparaginase in the treatment algorithm for ALL

Untreated ALL is fatal. Treatment is urgent, complex, often multimodal, and multidisciplinary. The choice of regimen is risk-based, with risk defined by clinical and laboratory features. Prognostic or risk groupings use age at diagnosis, WBC at diagnosis, cytogenetics and genomics of leukemia cells at diagnosis (favourable or unfavourable translocations) and response to therapy based on detection of minimal residual disease (MRD) after induction. The rapidity with which leukemia cells are eliminated and the level of residual disease are associated with long term outcome.

High intensity or paediatric protocols include the phases of remission induction, consolidation and maintenance, with treatment continuing over two to four years. Other regimens may be considered in older patients, or those with specifically targetable tumours.

Asparaginase appears in treatment algorithms for younger patients. The risk of adverse effects increases with increasing age. In Australia the currently available asparaginase is a pegylated E coli asparaginase (pegaspargase). The Australia eviQ guidelines carry precautionary statements against the use of pegaspargase in patients aged over 40 years because of the increased risk of toxicity.

Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

International regulatory status

Erwinaze (ERWINASE) was approved in 2011 by the FDA and EMA.

Jazz Pharmaceuticals was the commercial and distribution partner with Proton Biopharma Ltd PBL), the manufacturer of ERWINASE, including as the US Sponsor. The December 2020 these arrangements discontinued, and the US licenced product did not continue in the US market. In January 2021, PBL applied to the US FDA seeking approval of Erwinaze but received a Complete Response Letter on 22 November 2021 outlining significant quality issues and asking for either a clinical trial or modelling and simulation to confirm the chosen dosing regimen meets nadir serum asparaginase activity (NSAA) ≥0.1 IU/mL at the proposed dosing interval timepoint with >90% as the lower bound of the 95% confidence interval of the point estimate of the NSAA. Erwinaze is not currently approved for use in the USA.

Crisantaspase Porton Biopharma was approved in the Netherlands in October 2020 “based on Article 10(1) procedure. France, Ireland, and Portugal have issued national marketing authorisation through a mutual recognition procedure with the Netherlands as the reference

member state. Other signatory members states include Austria, Belgium, Germany, Finland, Spain and Poland. The wording of the indication is:

> *Crisantaspase Porton Biopharma is used in combination with other chemotherapeutic agents to treat patients, principally children, with acute lymphoblastic leukaemia who have developed hypersensitivity (clinical allergy or silent inactivation) to* E. coli *asparaginase or pegylated asparaginase obtained from* E. coli.

ERWINASE is not currently approved in Canada.

ERWINASE is approved by the MHRA for the following indication:

> *ERWINASE is indicated as a component of a chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E coli-derived asparaginase.*
>
> *ERWINASE is indicated in infants from the age of 4 months and in adults.*

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1. ERWINASE evaluation - Key dates

Description	Date
Submission dossier accepted and first round evaluation commenced	30 September 2021
First round evaluation completed	28 February 2022
Sponsor provides responses on questions raised in first round evaluation	31 March 2022
Second round evaluation completed	29 March 2023
Delegate's[5] Overall benefit-risk assessment and request for Advisory Committee advice.	31 October 2023
Advisory Committee meeting	December 2023
Registration decision (Outcome)	6 February 2024
Administrative activities and registration in the ARTG completed	14 February 2024
Number of working days from submission dossier acceptance to registration decision*	631

*Statutory timeframe for standard submissions is 255 working days

[5] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Submission overview and risk/benefit assessment

Quality

The quality Evaluators supported the registration of ERWINASE but recommended the imposition of conditions of registration. There are also post-approval commitments made by the Sponsor to the quality team that the Delegate intends to impose as conditions of registration.

The key features of the evaluation of the drug substance manufacture were:

- The drug substance contains primarily the native Erwinia L-Asparaginase which is a non-disulphide bonded, tetrameric protein consisting of four identical polypeptide chain subunits with a combined Molecular Weight of 140 kDa.
- The active ingredient was produced using native cell culturing. Information about the manufacturing, storage and control facilities for the active substance has been provided in the dossier.
- The Crisantaspase active substance is manufactured at Porton Biopharma Limited, Porton Down, England. The manufacturing process is a fermentation process with nutritive feeds. One vial of the working cell bank is thawed, and the cell culture is expanded in shake tubes and seeding bioreactors. The production bioreactor is harvested after a defined production period and an extraction is performed.
- The purification process includes three chromatography steps as well as viral inactivation/clearance steps, ultrafiltration/diafiltration, final formulation and final filtration (0.22 µm). The purification process has been described in sufficient detail, providing lists of process parameters and their acceptance criteria, for each step. Satisfactory elution profiles have been provided for the three chromatography steps.
- Crisantaspase active substance is stored in polyethylene bottles at -20°C and shipped to the finished product manufacturing facility at controlled conditions. Details including specifications and compatibility of the container, and a summary of an extractable and leachable study were presented and concluded that the risk for patients due to substances leaching into Crisantaspase active substance is negligible.
- The overall quality of the active substance was demonstrated via adequate control of the starting material, control of critical steps and intermediates, process validation, extensive characterisation, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

The key features of the evaluation of the drug product manufacture were:

- The formulation development has been adequately described and the final formulation intended for marketing was used in the phase III clinical trial. All excipients are well known pharmaceutical ingredients and their quality is compliant with USP standards. There are no novel excipients used in the finished product formulation. The container closure is considered suitable for its intended use as demonstrated by compatibility and stability studies.
- The finished product is manufactured at Baxter Oncology GmbH, Westphalia, Germany. The Crisantaspase finished product manufacturing process consists of active substance pooling, filtration through a 0.2 µm sterilizing grade filter, aseptic filling of the pre formulated active substance, freeze drying and visual inspection. All filled vials are visually checked, discarding those with defects. After the inspection process, the vials are stored at 5 ± 3°C pending

labelling and packaging. The description of the manufacturing process has been provided in sufficient detail.

- The finished product manufacturing process was developed with defined manufacturing procedures, process validations, critical process parameters, in-process parameters, batch analyses of multiple manufacturing campaigns. Finished product comparability studies were conducted to demonstrate that the quality of the commercial manufacturing process is comparable to the pre-change product. These were assessed and considered satisfactory by the quality Evaluator.
- All analytical methods used for testing of the finished product are satisfactorily described in the dossier and non-compendial methods have been validated. Many test methods used for release testing and stability testing of the finished product are the same as those used for release testing and stability testing of the active substance.
- The reference standard used in the testing and release of Crisantaspase finished product is the same as the one used for the testing and release of Crisantaspase active substance.
- The finished product presents in a 3 mL type I glass vial with halobutyl stopper and aluminium over-seal.
- The Evaluator was satisfied with stability data for the drug substance sufficient to support a shelf life of 12 months when stored at -20°C ± 5°C. The proposal is to store protected from light.
- The final product for release is a white lyophilised, solid white powder, that should reconstitute to a colourless solution essentially free from visible particles. It has a pH of 6.4 - 7. Each vial contains 10,000 IU of Crisantaspase . Excipients are sodium chloride, glucose ((dextrose monohydrate), acetic acid, and sodium hydroxide.
- The Evaluator had the following comments regarding specification and stability.
  - The finished product Quality Control for batch release includes identity, potency, purity, impurities, sterility (USP), bacterial endotoxin (USP) and several other general tests.
  - Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Following evaluation, the recommended storage condition is 36 months when stored at 5 ± 3°C.
  - In-use stability data have also been submitted. The recommended shelf life and storage conditions for the reconstituted product are 4 hours when stored at 25 ± 2°C.
  - The following temperature excursions from storage conditions are permitted: Store at 2-8°C with no more than 3 days (72 hours) at less than 25°C.
  - Stability studies have been conducted in accordance with relevant ICH guidelines.
  - The product is photostable.

The product must be reconstituted in 0.9% sodium chloride solution to achieve a final dose of 10,000 IU/mL. Following reconstitution for injection chemical and physical stability has been demonstrated for 15 minutes in the original container, and for 4 hours in a glass or polypropylene syringe, if stored below 25°C.

The reconstituted solution must be diluted prior to intravenous infusion. The diluted solution should be used immediately, from a microbiological perspective. Compatibility of the solution has been established with a polyvinylchloride infusion bag. The shelf-life has not been studied with any other kind of infusion bag.

Nonclinical

The nonclinical Evaluator found the studies in Module 4 data did not meet current nonclinical data requirements for new drug registration, such as consistency with current nonclinical ICH guidelines, and was overall considered of poor quality. The majority of the studies were conducted in the 1970s and the 1980s. Taking into account the long history of use, the Evaluator did not consider this finding precluded approval provided safety and efficacy were adequately demonstrated by clinical data.

Findings from the Module 4 component of the dossier are summarised below:

- Pharmacology studies in the nonclinical dossier included only literature describing E. coli asparaginase or mice.
- No specific invitro studies screening for off-target activity were submitted.
- No dedicated safety pharmacology studies were submitted by the Evaluator noted clinical central nervous system toxicity signs in moribund animals in the single dose and repeat dose toxicity studies that were submitted.
- From published studies the half-life with IV dosing in rats and monkeys was 1.5 to 2.6 hours, 10.4 to 15 hours in mice and rabbits and 7.5 to 16 hours in humans. No data for other PK parameters relating to tissue distribution, metabolism or excretion were included in the studies provided.
- The local tolerance studies in animals were not conducted using the proposed formulation for marketing. Local tolerance therefore relies on specific consideration from clinical studies.
- ERWINASE had a low level of acute toxicity in rodents but IV and IM dosing at clinical and subclinical doses did cause death in rabbits. Rabbits appeared to have a slower elimination of asparaginase and were sensitive to asparagine depletion. Rabbits have a higher circulating asparagine concentration compared to the other species and the clinical significance of the findings is uncertain.
- The repeat dose studies were insufficient to establish the toxicity profile of ERWINASE on a nonclinical basis. The evaluation found potential signals that could be of relevance for clinical safety. However, observations included hepatotoxicity in monkeys and rabbits, glucose intolerance/hyperglycaemia in monkeys and rabbits, weight loss in all species associated with reduced food consumption, emesis in dogs and monkeys, transient decrease in white blood cells in monkeys, and increases in urea and creatinine in monkeys and rabbits that was not correlated with renal pathology.
- The submission did not include genotoxicity studies, but this was acceptable and in accordance with ICH S6(R1)[6].
- No carcinogenicity studies have been conducted.
- No studies were conducted in juvenile animals. This was considered acceptable due to the long history of clinical use in paediatric patients.
- Based on submitted studies and published data on asparaginase, Crisantaspase is expected to be teratogenic. The Evaluator accepted the Sponsor's proposal that Crisantaspase should be Pregnancy Category D. The Sponsor recommends effective contraception during and for at least 3 months after completion of treatment with Crisantaspase .

[6] ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals – EMA Scientific guideline

- No studies specifically investigated the immunogenicity of ERWINASE or compared its immunogenicity to E. coli asparaginase. This was acceptable as immunogenicity in animals is not necessarily predictive of human immunogenicity.
- Asparaginases may inhibit lymphocyte blastogenesis based on in vitro studies and was shown to inhibit antibody responses in rat and mouse models.

Clinical

The three clinical studies in the submission are described in this section, including results for the primary endpoint. Relevant findings from each study are incorporated in the sections that follow.

Study AALL07P2

This was a single-arm, multicentre, open-label trial conducted between 2009 and 2010. It enrolled patients aged >1 year and ≤30 years with ALL who had ≥Grade 2 hypersensitivity to pegaspargase and who had ≥1 course of asparaginase remaining in their treatment protocol. Patients received 25,000 IU/m^2 intramuscularly either Monday/Wednesday/Friday, Wednesday/Friday/Monday, or Friday/Monday/Wednesday for a total of 6 doses to replace each dose of pegaspargase they were schedule to receive at the time of study entry.

This study had pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity and safety endpoints.

Of the 59 patients were enrolled, 58 received Erwinia asparaginase and 14 (24.1%) prematurely discontinued the study. Most patients completed the first and second course of treatment (96.5% and 75.9%, respectively). The median number of courses was 3. The maximum number of 9 courses was received by one patient.

The median age of patients was 11 years (2 to 18 years) and 59% were male. The mean BMI was 20.15 kg/m^2. The primary disease diagnosis was B-precursor ALL for 44 (74.5%) patients, T-cell ALL for 7 (12.7 %) patients, and ALL for 4 (7.3%) patients; 3 (5.5%) patients had a primary disease of “other.” All patients were within 9 months of diagnosis, with most within 6 months (94.8%).

Samples were collected after Dose 3 of the first course – 35 samples at the 48-hour timepoint and 13 samples at the 72-hour timepoint. The study samples were unsuitable for PD measurements and were used for PK and immunogenicity.

The primary objectives were to determine whether the 48-hour trough Serum Asparaginase Activity (SAA) was ≥0.1 IU/mL, as measured from a single 48-hour trough sample, and to characterise the toxicity and pharmacokinetics of Erwinia asparaginase. Determination of 72-hour SAA was a secondary endpoint. Results from the 48- and 72-hour timepoint measurements are summarised in the table below.

Table 2. Study AALL07P2: Serum Asparaginase Assay by Time Point

Table 14.2.1

Asparaginase Activity (IU/mL) by Time Point
PK Population

Time Point	N	Mean	Standard Deviation	%CV	Median	Minimum	Maximum
48 Hours	35	0.73	0.40	54.46	0.65	0.24	1.84
72 Hours	13	0.38	0.22	57.77	0.28	0.11	0.80

The main PK outcome and an exploratory analysis of the proportion of patients whose nadir SAA (NSAA) was ≥0.4 IU/mL are summarised below.

Table 3. Nadir Serum Asparaginase Activity at 48 hours and 72 hours after Intramuscular dosing

Trough sampling time post Dose 3	Main Outcome Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.1 IU/mL	Exploratory Analysis Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.4 IU/mL
48-hour	100% (35/35) 95% CI: 90%, 100%	80% (28/35) 95% CI: 64%, 90%
72-hour	100% (13/13) 95% CI: 77%, 100%	38% (5/13) 95% CI: 18%, 65%

Study 100EUSA12

This single arm, open label, multicentre pharmacokinetic study of intravenous Erwinaze following allergy to native E coli asparaginase, pegaspargase or calspargase pegol in 30 children, adolescents, and young adults with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma, conducted between 2012 and 2013.

The study enrolled patients aged 1 to 30 years who were undergoing asparaginase treatment for ALL/LBL and who had at least 2 consecutive remaining weeks of native E coli asparaginase treatment or at least one remaining dose of either pegaspargase or calaspargase pegol in their treatment plan. Most patients were male (63.3%), and the mean age was 7.9 (± 5.1 years). Most patients had B cell-precursor ALL (76.7%) and the remainder had T-cell ALL (20.0%) and LBL (3.3%).

Erwinia asparaginase 25,000 IU/m^2 given by IV infusion over 1 hour was dosed Monday/ Wednesday/Friday for up to 30 weeks. The protocol was amended to every other day dosing for a total of 7 days per 2-week course at the recommendation of the data safety monitoring board as a lower proportion of patients met the criteria for clinical efficacy at 72 hours after the 6th dose. Two patients changed to the every-other-day dosing regimen. A three weekly treatment regimen had been planned for patients changing from calaspargase pegol but no patients who enrolled in the study had been prescribed that medicine.

The study collected samples for pharmacokinetics, immunogenicity and collected safety events at specified timepoints and generally throughout the study.

Of the 30 patients who enrolled only 53.3% completed the study. Across the study 40.0% discontinued due to an adverse event (AE), and 33.3% due to a hypersensitivity reaction.

PK samples were provided by 24 patients.

Figure 1. Study 100EUSA12 Asparaginase Activity Levels vs Time after Start of Infusion by Course

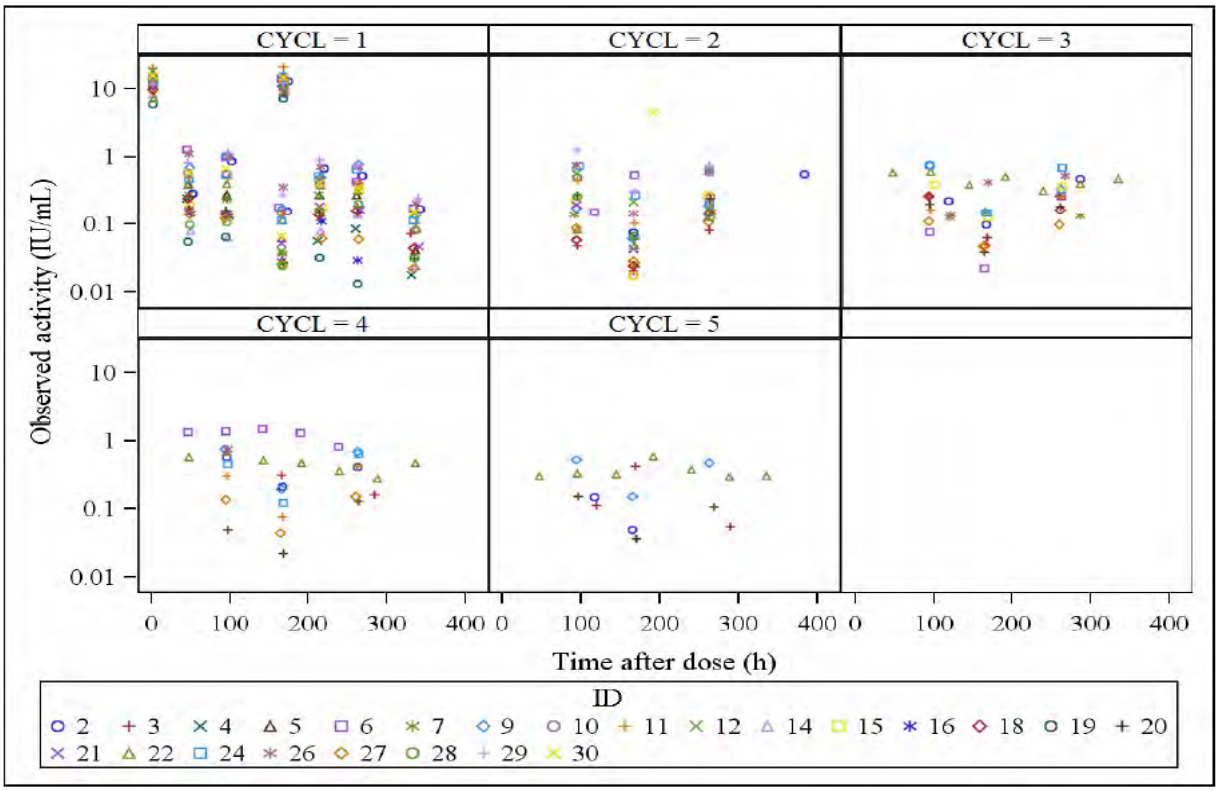


Table 4. Pharmacokinetic Results for Evaluable Patients – Course 1

	Dose 1			Dose 2	Dose 3	Dose 4		Dose 5	Dose 6
Timing Postdose	**0[a] (n=24)**	**5 min (n=22)**	**48 hr (n=19)**	**48 hr (n=23)**	**72 hr (n=21)**	**5 min (n=21)**	**48 hr (n=22)**	**48 hr (n=24)**	**72 hr (n=21)**
Mean (IU/mL)	-	12.65	0.37	0.42	0.09	12.10	0.32	0.32	0.09
±SD (IU/mL)	-	±3.16	±0.28	±0.36	±0.10	±3.11	±0.24	±0.23	±0.07
CV %	-	24.98	74.95	85.39	108.76	25.66	73.81	72.47	81.10
Range (IU/mL)	-	5.99–20.14	0.08–1.10	0.06–1.16	0–0.36	7.12–21.10	0.03–0.89	0.01–0.78	0–0.25
%Pts									
≥0.1 IU/mL	0	100	89	91	38	100	82	83	43
≥0.4 IU/mL	0	100	32	43	0	100	36	29	0

CV = coefficient of variation; LOD = limit of detection; Pt = patient(s); SD = standard deviation
n =number of evaluable patients

Table 5. Pharmacokinetic Results for Evaluable Patients in Courses 2 to 5

	Dose 1	Dose 2	Dose 3	Dose 5
Timing	Predose	48 hr Postdose	72 hr Postdose	48 hr Postdose
Course 2				
Evaluable patients	n = 19	n = 13	n = 16	n = 15
Mean ±SD (IU/mL)	–	0.43 ±0.336	0.09 ±0.096	0.28 ±0.207
%Pt ≥0.1 IU/mL	0%	85% (11/13)	31% (5/16)	93% (14/15)
%Pt ≥0.4 IU/mL	0%	46% (6/13)	0% (0/16)	20% (3/15)
Course 3				
Evaluable patients	n = 15	n = 7	n = 8	n = 9
Mean ±SD (IU/mL)	–	0.35 ±0.246	0.08 ±0.053	0.35 ±0.169
%Pt ≥0.1 IU/mL	0%	86% (6/7)	38% (3/8)	100% (9/9)
%Pt ≥0.4 IU/mL	0%	29% (2/7)	0% (0/8)	22% (2/9) (1/4)
Course 4				
Evaluable patients	n = 10	n = 9	n = 6	n = 6
Mean ±SD (IU/mL)	–	0.57 ±0.396	0.11 ±0.079	0.51 ±0.252
%Pt ≥0.1 IU/mL	0%	89% (8/9)	50% (3/6)	100% (6/6)
%Pt ≥0.4 IU/mL	0%	67% (6/9)	0% (0/6)	67% (4/6)
Course 5				
Evaluable patients	n = 6	n = 3	n = 2	n = 3
Mean ±SD (IU/mL)	–	0.33 ±0.184	0.096 ±0.083	0.32±0.190
%Pt ≥0.1 IU/mL	0%	100% (3/3)	50% (1/2)	100% (3/3)
%Pt ≥0.4 IU/mL	0%	33% (1/3)	0% (0/2)	33% (1/3)

SD = standard deviation; n =number of evaluable patients
Note: Denominator is number of evaluable patients as described in Section 9.7.1.1.
Course 6 PK data is not included as only 1 patient started Course 6 (Dose 1 only). PK data (Dose 1 48 hour, Dose 3 48 hour, Dose 4 48 hour, Dose 6 48 hour, and Dose 7 48 hour) for the 2 patients who followed the every-other-day dosing regimen once Protocol Amendment 2 was implemented are not included in the above table but are available in the source tables.

Pharmacology

Pharmacokinetics (PK)

The focus of the PK data in the submission is the measurement of serum asparaginase activity levels, considered to be a surrogate for asparagine depletion and thence clinical antitumour efficacy.

A number of publications described the PK of other forms of asparaginase. While of some interest these were not of direct relevance to the requested indication or dosing regimen.

Furthermore, the lower limit of quantification has changed over time.

The absorption and distribution kinetics were not well explained in the submission. Albertsen 2001[7] reported the bioavailability ranged from 11% to 61%, with a mean of 27% (SD 4.5%) with IM administration.

[7] Albertsen BK, Jakobsen P, Schrøder H, Schmiegelow K, Carlsen NT. Pharmacokinetics of Erwinia asparaginase after intravenous and intramuscular administration. Cancer Chemother Pharmacol. 2001 Jul;48(1):77-82. doi: 10.1007/s002800100286. PMID: 11488528.

Asselin 1993[8] found the half-life of Erwinia asparaginase was 16 hours, and asparagine depletion was up to 7- 15 days.

Metabolism and elimination of Erwinia asparaginase is assumed to be similar to other plasma proteins.

Half-life was estimated in several publications. The Evaluator tabulated the findings:

Table 6. Studies describing the half-life of Erwinia asparaginase.

Study Identifier	Erwinia asparaginase dose	Estimated half-life including PK model type if described)
Intramuscular administration		
Asselin 1993[9]	25,000 IU/m^2	15.6 ± 3.1 hr
Avramis 2007[10]	25,000 IU/m^2	One compartment model - 15.8±1.64 hours
Ogawa 2017[11]	25,000 IU/m^2	One compartment model – 13.4 ± 6.0 hr Non-compartment model - 16.9 ± 7.5 hr
Study AALL07P2	25,000 IU/m^2	Two compartment model - 16.5 ± 6.4 hr
Panetta 2020[12]*	30,000 IU/m^2	16.7 hrs
Intravenous administration		
Study 100EUSA12	25,000 IU/m^2	Two compartment model - 7.51 ± 1.80 hr
Albertsen 2001[13]	30,000 IU/m^2	6.4 +/- 0.5 hours
Panetta 2020[14]*	30,000 IU/m^2	16 hrs

*Accumulation or tachyphylaxis were not reported in the studies presented.

In the dedicated PK studies showed approximately 80%-100% of patients with IM dosing had an acceptable NSAA (either 0.1 or 0.4 IU/mL). With IV dosing no patients achieved a threshold of 0.41 IU/mL at 72 hours post dose, but at least 31% had a NSAA of 0.1 IU/mL.

No drug-drug interaction studies have been performed. Nevertheless, the PI includes information about drug-drug interactions.

[8] Asselin BL, Whitin JC, Coppola DJ, Rupp IP, Sallan SE, Cohen HJ. Comparative pharmacokinetic studies of three asparaginase preparations. J Clin Oncol. 1993 Sep;11(9):1780-6. doi: 10.1200/JCO.1993.11.9.1780. PMID: 8355045.

[9] ibid

[10] Avramis VI, Martin-Aragon S, Avramis EV, Asselin BL. Pharmacoanalytical assays of Erwinia asparaginase (erwinase) and pharmacokinetic results in high-risk acute lymphoblastic leukemia (HR ALL) patients: simulations of erwinase population PK-PD models. Anticancer Res. 2007 Jul-Aug;27(4C):2561-72. PMID: 17695416.

[11] Ogawa C, Taguchi F, Goto H, Koh K, Tomizawa D, Ohara A, Manabe A. Plasma asparaginase activity, asparagine concentration, and toxicity after administration of Erwinia asparaginase in children and young adults with acute lymphoblastic leukemia: Phase I/II clinical trial in Japan. Pediatr Blood Cancer. 2017 Sep;64(9). doi: 10.1002/pbc.26475. Epub 2017 Feb 28. PMID: 28244643.

[12] Panetta JC, Liu Y, Swanson HD, Karol SE, Pui CH, Inaba H, Jeha S, Relling MV. Higher plasma asparaginase activity after intramuscular than intravenous Erwinia asparaginase. Pediatr Blood Cancer. 2020 Jul;67(7):e28244. doi: 10.1002/pbc.28244. Epub 2020 Apr 23. PMID: 32323890; PMCID: PMC7253324.

[13] Albertsen BK, Jakobsen P, Schrøder H, Schmiegelow K, Carlsen NT. Pharmacokinetics of Erwinia asparaginase after intravenous and intramuscular administration. Cancer Chemother Pharmacol. 2001 Jul;48(1):77-82. doi: 10.1007/s002800100286. PMID: 11488528

[14] Panetta 2020

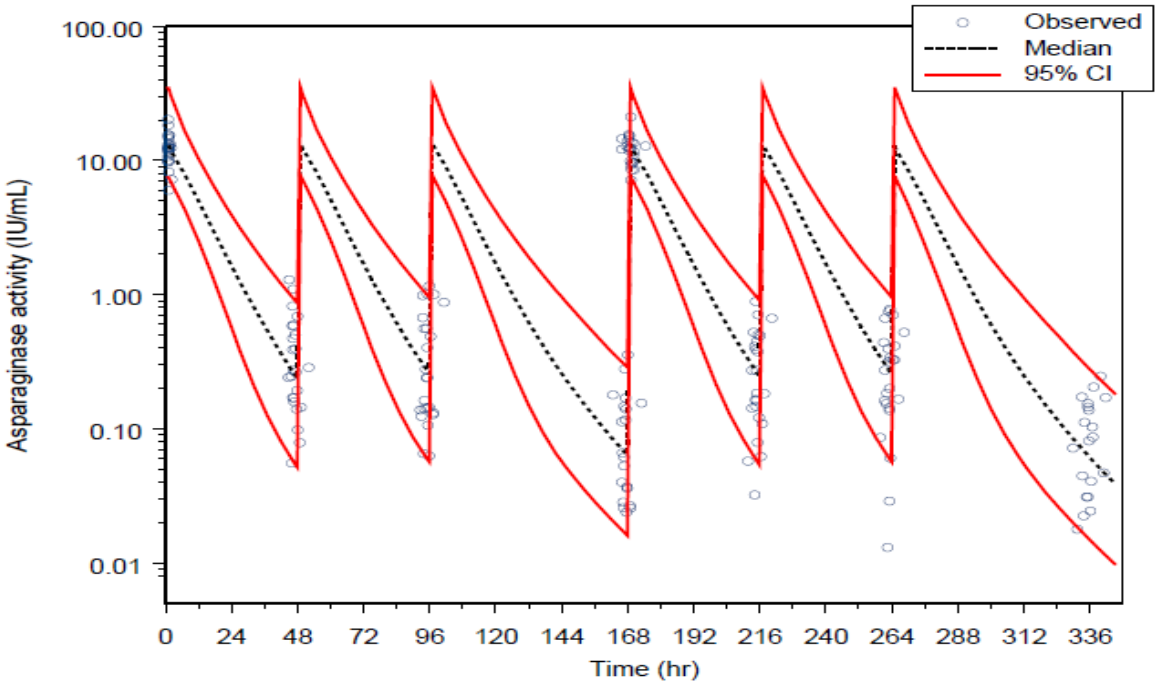
Population PK data (popPK)

A pharmacometrics analysis was conducted using data from Study 100EUSA12.

A two-compartment model best fit the data following IV administration. The analysis of covariates found that only weight had a statistically significant effect. Using the model, calculated PK parameters were: mean clearance (CL) 156.92, (SD 45.24) ml/hr; mean volume of distribution (central compartment) 1594 ml; mean volume of distribution (peripheral compartment) 154ml; mean half-life 7.51 (SD 1.80) hours; median half-life 7.16 hours.

Simulated asparaginase activity levels against time curves (see below) demonstrate the lower trough following the third (dose) with administration on Mon/Wed/Fri for 2 weeks.

Figure 2. Final Covariate Model Log Asparaginase Activity vs. Serial Time (Cycle 1 Only)



A PopPK analysis of data from Study AALL07P2 was not included in the submission for evaluation.

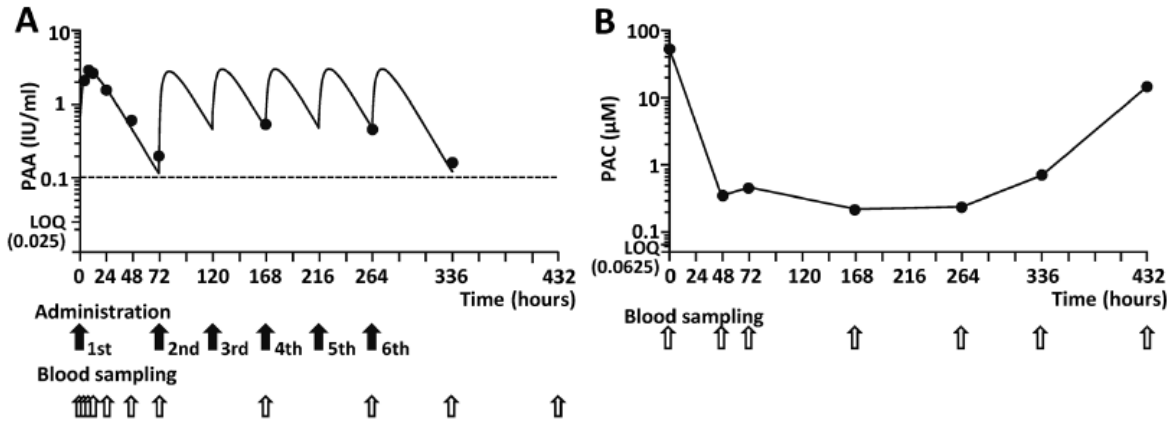
Pharmacodynamics

The anticancer activity of asparaginases is attributed to the enzymatic depletion of asparagine in plasma and CSF and glutamine, that are converted to aspartic acid and glutamic acid. Under normal physiological conditions, circulating asparaginase concentrations range between 40 and 80 µM. Although no formal criterion exists, complete asparagine depletion has been defined as less than 0.1 – 0.2 µM based on the limit of detection of the high-performance liquid chromatography assay used. However, the critical level of asparagine depletion in serum required for in *vivo* leukemic cell death is unknown.

The measurement of serum asparagine is challenging because asparaginase present in specimens can continue the breakdown of asparagine *ex vivo* if the specimen is not processed immediately and stored on ice.

Ogawa 2017[15] reported plasma activity and plasma asparagine concentrations in 23 Japanese children and young adults (ages 1 – 25 years) who received Erwinia asparaginase 25,000IU/m^2 IM on alternate days for a 2-week period. The LLQ for plasma asparaginase was 0.0625 µM.

Figure 3. Mean plasma asparaginase activity (PAA) and mean plasma asparagine concentration (PAC) versus time with 6 doses of 25,000 IU/m^2 of Erwinia asparaginase IM (from Ogawa 2017)



Pharmacokinetics of Erwinia asparaginase. (A) Mean Plasma Asparaginase Activity (PAA)–time profile for the six 25,000 IU/m^2 intramuscular administrations. Administrations of asparaginase and blood collections were performed at times indicated. The continuous line is the best-fit curve determined by nonlinear regression analysis of the mean profile. (B) Mean Plasma Asparagine Concentration (PAC)–time profile

Viera Pinheiro 1999[16], Tong 2014b[17] and Rizzari 2000[18] (using a LLQ of 0.2µM for L-asparagine) found asparagine levels below the LLQ at sampling coinciding with trough concentrations of asparaginase in patients receiving 10,000 IU and 20,000 IU dosing regimens of Erwinia asparaginase.

The submission included literature describing apparent dose response relationships for efficacy and safety based on asparaginase levels for two different formulations of *E coli* derived asparaginase.

Schrey 2011[19] included data from 127 patients with ALL collected over a 5-year period. The patient cohort included standard medium and high-risk patients who switched to ERWINASE from *E coli* derived asparaginase formulations but analyses specifically for ERWINASE were not included in the publication.

An analysis of trough asparaginase activity levels during induction and Minimal Residual Disease (MRD) findings at Day 33 in patients receiving *E coli* asparaginase 5000 IU/m^2 found median

[15] Ogawa 2017

[16] Vieira Pinheiro JP, Ahlke E, Nowak-Göttl U, Hempel G, Müller HJ, Lümkemann K, Schrappe M, Rath B, Fleischhack G, Mann G, Boos J. Pharmacokinetic dose adjustment of Erwinia asparaginase in protocol II of the paediatric ALL/NHL-BFM treatment protocols. Br J Haematol. 1999 Feb;104(2):313-20. doi: 10.1046/j.1365-2141.1999.01192.x. PMID: 10050714.

[17] Tong WH, Pieters R, Kaspers GJ, te Loo DM, Bierings MB, van den Bos C, Kollen WJ, Hop WC, Lanvers-Kaminsky C, Relling MV, Tissing WJ, van der Sluis IM. A prospective study on drug monitoring of PEG asparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. Blood. 2014 Mar 27;123(13):2026-33. doi: 10.1182/blood-2013-10-534347. Epub 2014b Jan 21. PMID: 24449211; PMCID: PMC3968389.

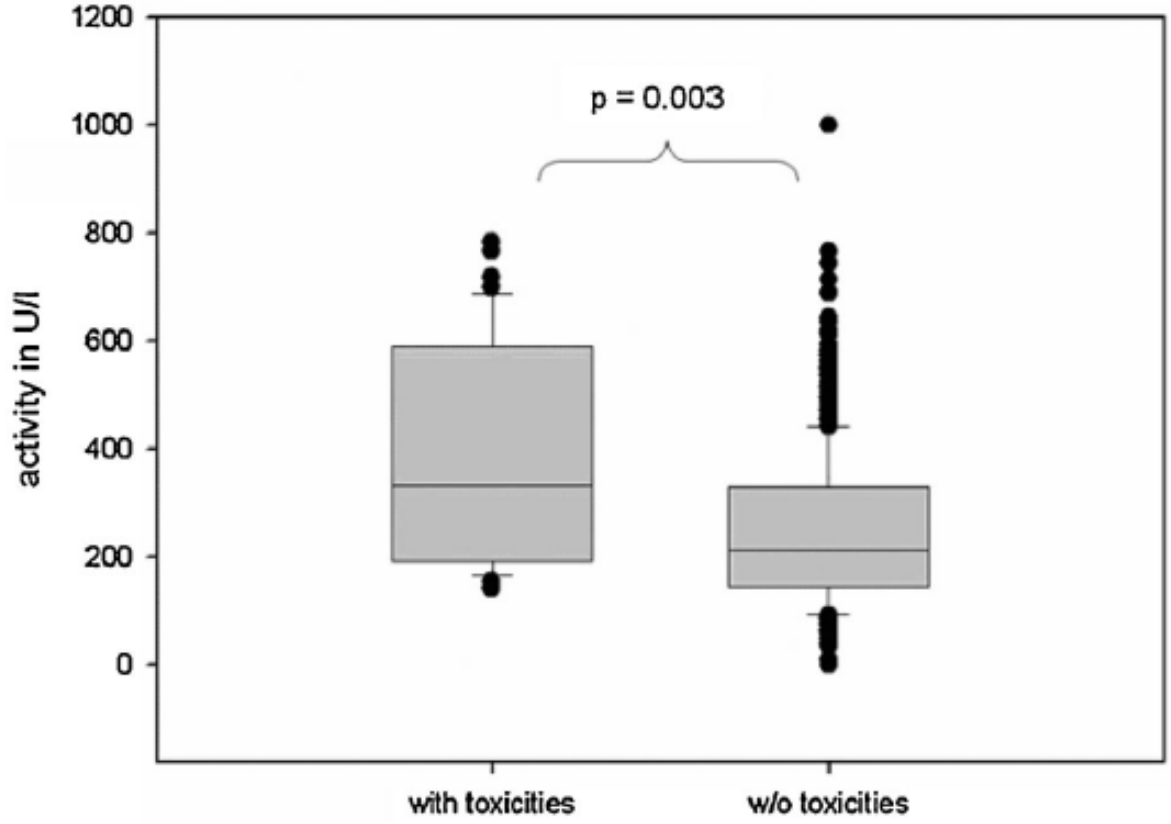
[18] Rizzari C, Zucchetti M, Conter V, Diomede L, Bruno A, Gavazzi L, Paganini M, Sparano P, Lo Nigro L, Aricò M, Milani M, D'Incalci M. L-asparagine depletion and L-asparaginase activity in children with acute lymphoblastic leukemia receiving i.m. or i.v. Erwinia C. or E. coli L-asparaginase as first exposure. Ann Oncol. 2000 Feb;11(2):189-93. doi: 10.1023/a:1008368916800. PMID: 10761754

[19] Schrey D, Speitel K, Lanvers-Kaminsky C, Gerss J, Möricke A, Boos J. Five-year single-center study of asparaginase therapy within the ALL-BFM 2000 trial. Pediatr Blood Cancer. 2011 Sep;57(3):378-84. doi: 10.1002/pbc.23041. Epub 2011 Feb 18. PMID: 21337682

trough asparaginase activity levels for MRD negative patients and MRD positive patients were 216 U/L [range: (44–744 U/L)] and 225 U/L [range: (0–784 U/L)]; p = 0.63, respectively.

Asparaginase activity related toxicity was reported. Toxicity events of interest were pancreatitis, thromboembolic events, hyperglycaemia, coagulopathy, impaired liver synthesis and hepatotoxicity. Asparaginase activity values measured in the samples from patients with severe toxicity (range142–784 U/L) from patients without toxicity (range <2.5–1,000 U/L). The median asparaginase activity at Day 3 after the administration was significantly higher than the median activity in 111 patients (596 samples) without documented severe toxicity (332 U/L vs. 214 U/L; P = 0.003).

Figure 4. *E coli* Asparaginase activity and toxicity. Asparaginase activity at day +3 after administration of 5000U/m² E. Coli ASNase during induction in relation to severe ASNase related toxicities (Mann-Whitney Rank Sum Test, P=0.003).



Rizzari 2001[20] reported findings from 610 intermediate risk ALL patients who were in complete response at the commencement of the re-induction phase of treatment who were randomised to either high dose or standard dose treatment. Around 90% of patients received ERWINASE because of an *E coli* asparaginase shortage. Dosing was 10,000 IU/m² (standard dose) or 25,000 IU/m² (high dose). Of the treated patients, 9/126 patients (7%) discontinued because of toxicities in the high dose group (hypersensitivity n=5, prolonged myelosuppression n=2, seizures n=1, liver dysfunction n=1) but only 1/119 patients (0.8%) discontinued in the standard dose group, although the reason for discontinuation was not reported.

Asparaginases act on extracellular glutamine, and possibly reductions in glutamine and asparagine are both needed for efficacy. Glutamine is thought to be the main amino group donor

[20] Rizzari, 2001 (n 15)`

for intracellular asparagine synthesis from aspartate. Jarrar 2006[21] found a relationship between favourable bone marrow response and lower glutamine level at the end of induction with PEG asparaginase.

Panosyan 2004[22] modelled the depletion of asparagine and glutamine and found that asparaginase activity <0.1 IU/mL provided insufficient depletion of asparagine and glutamine. Adequate asparagine depletion (<3μM) with an average asparaginase activity of 0.11 IU/mL was observed in 24/121 post-treatment samples.

Literature and the Sponsor's studies support that asparaginase inhibits liver protein synthesis. The mechanism is thought to be asparagine and possible glutamine depletion. Affected proteins include fibrinogen, prothrombin, protein C, antithrombin III, plasminogen and albumin, which were depleted during Erwinia asparaginase treatment (Albertsen 2001[23], with concordant findings in Study AALL07P2). Reduced plasma proteins are thought to result from an interaction between glucocorticoids and asparagine, possibly potentiating hyperglycaemia, as well as the hypertriglyceridemia and hypercholesterolaemia found with prolonged use (Tong 2014a)[24].

Immunogenicity

The two clinical studies and a number of the publications included information about the occurrence of anti-Erwinia-asparaginase antibodies (ADAs).

It is not clear that the same assays and sampling strategies were used in all studies (literature and submitted studies) for the determination of the presence of ADAs adding some uncertainty about any conclusions drawn.

In Study AALL07P2, 56/58 patients were screened, and 11% patients (6 patients) had confirmed ADAs at ≥1 timepoint during treatment, and one experienced a hypersensitivity reaction after two courses of treatment, resulting in treatment discontinuation. Two patients transiently developed neutralising antibodies but had asparaginase activity within the range of the overall population.

In Study 100EUSA12, all patients were screened and 13% (4 patients) were ADA positive, none had neutralising antibodies but 3/4 withdrew from the study after experiencing hypersensitivity reactions.

Albertsen 2002[25] reported 9/19 patients receiving re-induction treatment including Erwinia asparaginase developed ADAs. Four of those patients had very low asparaginase levels, presumed related to neutralising antibodies. None of these patients developed an overt hypersensitivity reaction.

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[21] Jarrar M, Gaynon PS, Periclou AP, Fu C, Harris RE, Stram D, Altman A, Bostrom B, Breneman J, Steele D, Trigg M, Zipf T, Avramis VI. Asparagine depletion after pegylated E. coli asparaginase treatment and induction outcome in children with acute lymphoblastic leukemia in first bone marrow relapse: a Children's Oncology Group study (CCG-1941). Pediatr Blood Cancer. 2006 Aug;47(2):141-6. doi: 10.1002/pbc.20713. PMID: 16425271.

[22] Panosyan EH, Grigoryan RS, Avramis IA, Seibel NL, Gaynon PS, Siegel SE, Fingert HJ, Avramis VI. Deamination of glutamine is a prerequisite for optimal asparagine deamination by asparaginases in vivo (CCG-1961). Anticancer Res. 2004 Mar-Apr;24(2C):1121-5. PMID: 15154634

[23] Albertsen BK, Jakobsen P, Schrøder H, Schmiegelow K, Carlsen NT. Pharmacokinetics of Erwinia asparaginase after intravenous and intramuscular administration. Cancer Chemother Pharmacol. 2001 Jul;48(1):77-82. doi: 10.1007/s002800100286. PMID: 11488528

[24] Tong WH, Pieters R, de Groot-Kruseman HA, Hop WC, Boos J, Tissing WJ, van der Sluis IM. The toxicity of very prolonged courses of PEGasparaginase or Erwinia asparaginase in relation to asparaginase activity, with a special focus on dyslipidemia. Haematologica. 2014 Nov;99(11):1716-21. doi: 10.3324/haematol.2014.109413. Epub 2014[a] Aug 22. PMID: 25150254; PMCID: PMC4222477

[25] Albertson, B., Schroder, H, Jakobsen, P, et al. Antibody Formation During Intravenous and Intramuscular Therapy with Erwinia Asparaginase. Med Pediatr Oncol 2002; 38:310-316

A review of the literature did not reveal evidence of direct cross-reactivity between hypersensitivity *E coli* asparaginase with or without ADAs and Erwinia asparaginase, although patients can develop hypersensitivity to both types of asparaginase.

Efficacy

The Evaluator found there was limited evidence in the submission to support the clinical efficacy of Crisantaspase for the proposed indication, dose and dosing regimen. The Evaluator summarised the main evidence in the table below:

Table 7. Summary of Clinical Evidence Related to Clinical Outcome

Study identifier	Use	Dosing regimen	EFS/DFS	OS
Eden 1990[26]	First line	6000 IU/m^2, 3x per week for 9 doses	No significant difference compared to *E. coli* asparaginase	NR
Duval 2002[27]	First line	10000 IU/m^2 weekly for 12 weeks	59.8% at 6 years	75.1% at 6 years
Moghrabi 2007[28]	First line	25000 IU/m^2 weekly	78% at 5 years	NR
Vrooman 2010[29]	Substitution	25000 IU/m^2 twice weekly	86% at 5-year follow-up	NR
Rizzari 2001[30]	First line	Standard dose -10000 IU/m^2 x 4 doses over three weeks	72.4% at 7 years	NR
		High dose – 25000 IU/m^2 weekly for 20 weeks	75.7% at 7 years	

[26] Eden, O.B., Shaw, M.P., Lilleyman, J.S. and Richards, S. (1990), Non-randomised study comparing toxicity of escherichia coli and erwinia asparaginase in children with leukaemia. Med. Pediatr. Oncol., 18: 497-502. https://doi.org/10.1002/mpo.2950180612

[27] Duval M, Suciu S, Ferster A et al for the European Organisation for Research and Treatment of Cancer—Children's Leukemia Group, Comparison of Escherichia coli–asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer—Children's Leukemia Group phase 3 trial. Blood 2002; 99 (8): 2734–2739. doi: https://doi.org/10.1182/blood.V99.8.2734

[28] Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood. 2007 Feb;109(3):896-904. DOI: 10.1182/blood-2006-06-027714. PMID: 17003366; PMCID: PMC1785142.

[29] Vrooman LM, Stevenson KE, Supko JG, O'Brien J, Dahlberg SE, Asselin BL, Athale UH, Clavell LA, Kelly KM, Kutok JL, Laverdière C, Lipshultz SE, Michon B, Schorin M, Relling MV, Cohen HJ, Neuberg DS, Sallan SE, Silverman LB. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol. 2013 Mar 20;31(9):1202-10. doi: 10.1200/JCO.2012.43.2070. Epub 2013 Jan 28. PMID: 23358966; PMCID: PMC3595424.

[30] Rizzari, 2001.

Study identifier	Use	Dosing regimen	EFS/DFS	OS
Yen 2016[31]	Substitution	A dose 2 to 5× that of *E. coli* asparaginase	64% at 5 years	88% at 5 years
Schmidt 2021[32]	Substitution	10000 IU/m^2 every 3 days for 8 doses during induction. Further doses during consolidation and maintenance according to risk	77.5% at 5 years*	86.2% at 5 years
Gupta 2020[33]	Substitution (PEG asparaginase)	25000 IU/m^2, 6 doses over two weeks	Reported as Hazard ratios for the group to group comparisons: Standard risk patients – no difference in EFS and OS between patients switching to Erwinia asparaginase or patients who did not complete course compared to patients competing PEG asparaginase; High risk patients - no difference in OS between patients switching to Erwinia asparaginase or patients who did not complete course compared to patients completing PEG asparaginase; inferior DFS in patients who did not complete asparaginase compared to patients completing PEG asparaginase; no significant difference between patients switching to Erwinia asparaginase compared to patients completing PEG asparaginase	

[31] Yen HJ, Chang WH, Liu HC, Yeh TC, Hung GY, Wu KH, Peng CT, Chang YH, Chang TK, Hsiao CC, Sheen JM, Chao YH, Chang TT, Chiou SS, Lin PC, Wang SC, Lin MT, Ho WL, Chen YC, Liang DC. Outcomes Following Discontinuation of E. coli l-Asparaginase Upon Severe Allergic Reactions in Children With Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2016 Apr;63(4):665-70. doi: 10.1002/pbc.25869. Epub 2015 Dec 24. Erratum in: Pediatr Blood Cancer. 2016 Jun;63(6):1131. PMID: 26703788.
[32] Schmidt MP, Ivanov AV, Coriu D, Miron IC. L-Asparaginase Toxicity in the Treatment of Children and Adolescents with Acute Lymphoblastic Leukemia. J Clin Med. 2021;10(19):4419. Published 2021 Sep 26. doi:10.3390/jcm10194419
[33] Gupta S, Wang C, Raetz EA, et al. Impact of Asparaginase Discontinuation on Outcome in Childhood Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. J Clin Oncol. 2020 Jun 10;38(17):1897-1905. doi: 10.1200/JCO.19.03024. Epub 2020 Apr 10. PMID: 32275469; PMCID: PMC7280050.

Study identifier	Use	Dosing regimen	EFS/DFS	OS
EFS – event free survival; DFS – disease free survival; NR – not reported; OS – overall survival * Reported for patients who developed hypersensitivity to PEG asparaginase, not all of whom received Erwinia asparaginase				

Substitution studies are considered of most relevance to the second-line nature to the proposed indication. Gupta *et.al.* 2020, substituted with the proposed dose for registration and is therefore considered in more detail than the other substitution studies.

Gupta et.al. 2020[34]

The study by Gupta *et.al.* includes efficacy data from use of an Erwinia asparaginase at the proposed dose.

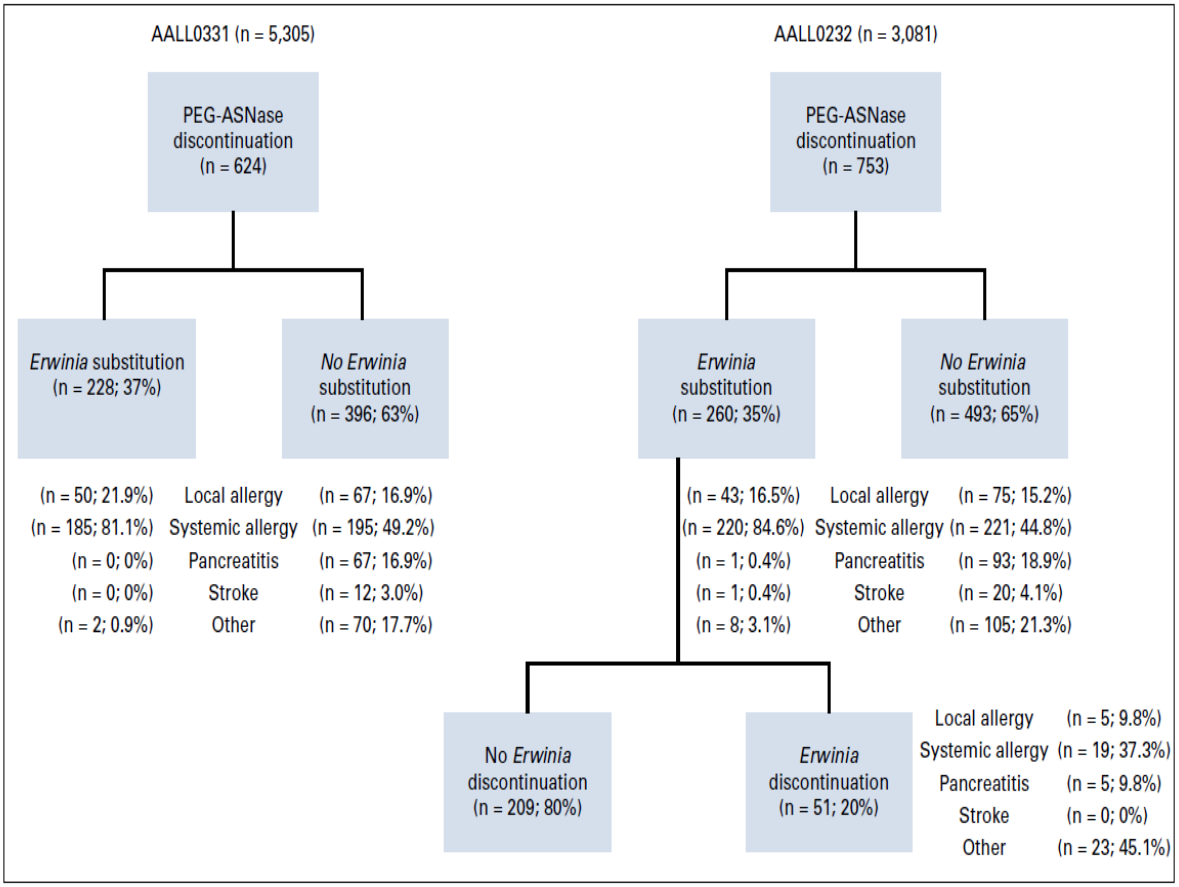
The publication described data from Studies ALL0331 and ALL0232, and included data accrued between 2004 and 2011. Patients in these trials received PEG asparaginase (2,500 IU/m^2) in accordance with Dana-Farber Cancer Institute (DFCI) ALL protocols. The number of planned doses of PEG asparaginase varied according to risk group and chemotherapy backbone intensity, with high-risk patients receiving 9 to 11 doses. If PEG asparaginase hypersensitivity developed, patients were to switch to Erwinia asparaginase at the replacement schedule of 6 doses (25,000 IU/m^2 intramuscularly) on Monday, Wednesday, and Friday, for each PEG-asparaginase dose.

Study data from 5,305 standard risk and 3,081 high-risk patients were included.

During the studies there were periods during which Erwinia asparaginase was not available and 1377 patients across the two studies either had PEG asparaginase hypersensitivity and did not receive any asparaginase treatment (889 patients) or had Erwinia asparaginase hypersensitivity or other toxicities discontinued the treatment (488 patients) (Figure 5).

[34] ibid

Figure 5. Number of patients experiencing pegaspargase (PEG-ASNase) discontinuation and the reasons for discontinuation.

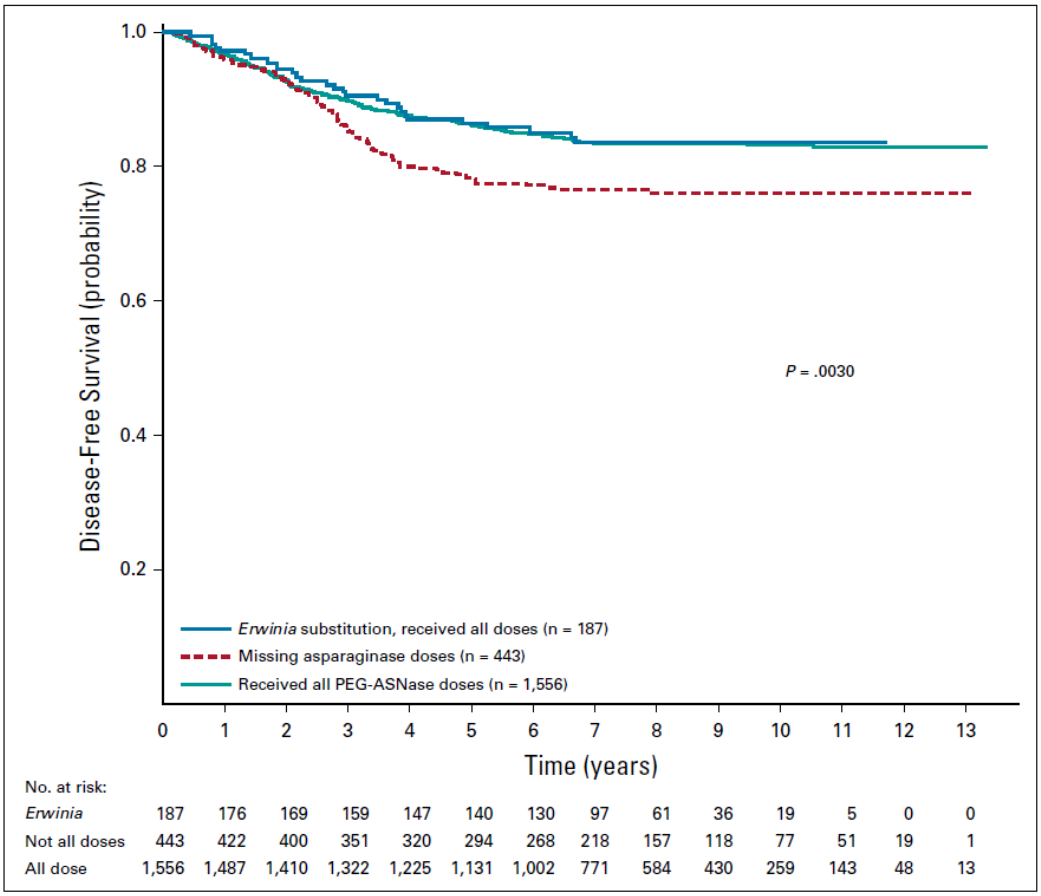


Multivariate analyses found that:

- For all standard risk patients
  - after failure to complete all prescribed doses the disease-free survival (DFS) hazard ratio [HR] was 1.2 (95% CI, 0.9 to 1.6) compared to patients who received all PEG asparaginase doses
  - after failure to complete all prescribed doses the overall survival (OS) HR was 1.2 (95% CI, 0.7 to 1.8) compared to patients who received all PEG asparaginase doses
- For patients with standard risk-high (Study AALL0331) (defined as patients with "slow early response" according to Day 15 blast count or Day 29 MRD)
  - after failure to complete all prescribed doses the DFS HR was 1.7 (95% CI, 1.0 to 2.6) compared to patients who received all PEG asparaginase doses
  - after failure to complete all prescribed doses, the OS HR was 1.6 (95% CI, 0.8 to 3.2) compared to patients who received all PEG asparaginase doses
- For high-risk patients (Study AALL0332)
  - after PEG asparaginase substitution with Erwinia asparaginase with all doses completed the DFS HR was 1.1 (95% CI, 0.8 to 1.7) compared to patients who did not discontinue PEG asparaginase
  - after failure to complete all prescribed doses the DFS HR was 1.5 (95% CI, 1.1 to 1.9) compared to patients who received all PEG asparaginase doses

- When patients discontinuing asparaginase for either pancreatitis or thrombosis were excluded, the patients who did not receive all prescribed asparaginase the DFS HR was 1.4 (95% CI, 1.1 to 1.8)
- after PEG asparaginase substitution with Erwinia asparaginase with all doses the OS HR 0.8 (95% CI, 0.4 to 1.4) compared to patients who did not discontinue PEG asparaginase
- after failure to complete all prescribed doses, the OS HR was 1.2 (95% CI, 0.9 to 1.8) compared to patients who received all PEG asparaginase doses

Figure 6. Disease Free Survival in the High-Risk Patient Group



The Evaluator concluded that there was benefit in switching to Erwinia asparaginase in patients who develop allergy to *E coli* asparaginase if they have high risk disease, but the benefit appears to be limited to disease free survival.

***Vrooman 2010*[35]**

Although this was primarily a PK and tolerability study of Erwinia asparaginase when used as a substitute for E coli asparaginase, and included10 patients with a double switch from E coli asparaginase to Erwinia asparaginase (25,000 IU/m^2, twice weekly) to PEG asparaginase (because of a shortage of Erwinia asparaginase). At a median follow-up of 5.4 years, EFS (± standard error) for the 42 patients who switched to *Erwinia* asparaginase was 86 ± 5% in comparison to 81% ± 3% for the 170 patients without *E coli* asparaginase allergy (p=0.55 by the log rank test).

[35] Vrooman 2010 (n 26)

Yen 2016[36]

This article reports outcomes of 700 Taiwanese children (age <18 years) with newly diagnosed ALL in whom native *E. coli* asparaginase was discontinued due to severe allergic reactions compared to patients who were able to complete planned asparaginase doses.

All patients were treated according to the Taiwan Paediatric Oncology Group (TPOG)-2002-ALL protocol. *E. coli* asparaginase was administered IM during different phases of treatment:

- remission induction phase - 5,000 IU/m^2 per dose three times weekly for 3 weeks
- continuation therapy - 10,000 IU/m^2 per dose weekly for 20 weeks
- reinduction cycle - 5,000 IU/m^2 per dose three times weekly for 2 weeks

Patients with standard risk ALL, received asparaginase during continuation therapy and were randomised to receive one or two re-induction cycles. Patients with very high-risk disease received asparaginase during remission induction, continuation therapy and one re-induction cycle.

If patients developed a severe allergic reaction or other serious adverse event necessitating discontinuation of *E coli* asparaginase, Erwinia asparaginase was used to substitute in some patients. In patients who were unable to switch to Erwinia asparaginase, an intramuscular injection of methotrexate (40 mg/m^2) was given on a weekly basis during the period of each previously scheduled *E coli* asparaginase treatment.

There were no apparent differences in baseline characteristics of patients who did and did not develop allergies to *E coli* asparaginase.

Of the 52 patients who discontinued, 33 were due to severe allergic reactions, and of those 17 received ERWINASE "*at a dosage of two- to fivefold (a median of fourfold) that of E. coli asparaginase dosage*", while the remainder received no further asparaginase treatment. The remainder discontinued due to other adverse events.

Of the patients with allergic reactions who switched or received no asparaginase there were no significant difference for event free survival or overall survival, however the groups were small and estimates of effect lacked precision. The authors noted that most patients had received most of their scheduled *E coli* asparaginase treatment prior to the severe allergic reaction.

Schmidt 2021[37]

This retrospective analysis of 165 patients with ALL treated with a multiagent chemotherapy protocol containing native *E coli* asparaginase were managed in a single centre between 2010 and 2019. Hypersensitivity was reported in 40 patients of whom 19 switched to Erwinia asparaginase, 10 switched to PEG asparaginase, and 11 discontinued treatment. Of those who discontinued, 7 had a cumulative dose of ≥50% of the scheduled dose. The choice of alternative asparaginase appeared to be related to availability.

After a median duration of follow up of 5 years (0.1 – 11.5 years) OS was 86.2% in those switching and 72.2% in those discontinuing their initial asparaginase (p=0.29). EFS was 77.5% for those switching or discontinuing and 71.8% without hypersensitivity (and a switch).

Safety

Safety data were collected in studies AALL07P2, 100EUSA12, and the Erwinaze Master Treatment Protocol (EMTP). The submission included three Period Benefit Risk Evaluation

[36] Yen 2016 (n 28)

[37] Schmidt 2021 (n 29)

Reports (PBRERs) and published literature. The CER includes summaries of these data and commentary on the findings.

All adverse events were required to be reported in study AALL07P2, but studies 100EUSA12 and EMTP required only the collection of solicited adverse events. The reporting of safety was not uniform or systematic across the published literature. The denominator of total patients exposed, or the duration of exposure for all patients is unknown for the total safety set.

Patient exposure was provided for studies AALL07PR and 100EUSA12: 94.8% and 86.7% respectively received at least 1 course of Erwinia asparaginase. In study AALL07P2 27.6% and 16.7% of studies AALL07PR and 100EUSA12 patients completed 5 courses of therapy. Up to 4 further courses were completed in study AALL07P2.

The mean ages of enrolled patients in the three clinical studies were 7.9 to 10 years, but the ages ranged from <1 year to 76 years). The EMTP included 35 patients aged > 21 years, of whom 14 were aged ≥30 years. Around 60% were male and 79.5% were white. Most (75%) had B-cell ALL. LBL was the diagnosis in 32 patients in study EMTP and one in study100EUSA12.

Table 8. Summary of Adverse Events of Studies AALL07P2, 100EUSA12 and EMTP

	Study AALL07P2 **N = 58** **n (%)**	**Study EMTP** **N = 940** **n (%)**	**Study 100EUSA12** **N = 30** **n (%)**
Patients with any TEAE	22 (37.9)	340 (36.2)	23 (76.7)
Patients with related TEAE	20 (34.5)	170 (18.1)	16 (53.3)
Patients with Grade 3 or higher TEAE	17 (29.3)	144 (15.3)	14 (36)
Patients with any SAE	19 (32.8)	281 (29.9)	15 (50.0)
Patients who discontinued due to TEAE	7 (12.1)	122 (13.0)	12 (40)
Patients with TEAE resulting in death	0	18 (1.9)	0

In these studies, the most commonly reported TEAEs in the three studies are summarised below.

Table 9. Common Treatment Emergent Adverse Events in AALL07P2, EMTP and 100EUSA12

Preferred Term	Study AALL07P2 N = 58 n (%)	Study EMTP N = 940 n (%)	Study 100EUSA12 N = 30 n (%)
Hypersensitivity	8 (13.8)	131 (13.9)	10 (33.0)
Nausea	2 (3.4)	23 (2.4)	7 (23.3)
Vomiting	3 (5.2)	27 (2.9)	6 (20.0)
Hyperglycemia	7 (12.1)	33 (3.5)	5 (16.7)
Febrile neutropenia	4 (6.9)	20 (2.1)	4 (13.3)
Hyperbilirubinemia	6 (10.3)	3 (0.3)	0
Aspartate aminotransferase increased	6 (10.3)	18 (1.9)	1 (3.3)
Pyrexia	2 (3.4)	35 (3.7)	3 (10.0)
Neutropenia	5 (8.6)	14 (1.5)	0
Alanine aminotransferase increased	5 (8.6)	30 (3.2)	3 (10.0)
Pancreatitis	1 (1.7)	34 (3.6)	2 (6.7)
Stomatitis	0	1 (0.1)	2 (6.7)
Sepsis	3 (5.2)	10 (1.1)	1 (3.3)

Studies 100EUSA12 and EMTP provided a breakdown of the commonly occurring Grade 3 or 4 AEs as follows:

Table 10. Common Grade 3 or 4 Events in Studies 100EUSA12 and EMTP

	Study 100EUSA12 N=30 n (%)	**Study EMTP N=940 n (%)**
Number of patients with one or more ≥ grade 3 AE	10 (33)	140 (14.9)
Hypersensitivity	0	34 (3.6)
Anaphylaxis	0	8 (0.9)
Hyperglycaemia	1 (3.3)	33 (3.5)
Febrile neutropenia	4 (13.3)	14 (1.5)
Pancreatitis	2 (6.6)	8 (0.9)
Stomatitis	2 (6.6)	

Most events considered to be treatment related are also events known to be associated with Crisantaspase use and included in the list of adverse events of special interest.

Table 11. Adverse events of Special Interest – Studies AALL07P2, 100EUSA12 and EMTP

Collated Term	Study AALL07P2 N = 58 n (%)	Study EMTP N = 940 n (%)	Study 100EUSA12 N = 30 n (%)
Hypersensitivity	8 (13.8)	128 (13.6)	10 (33.3)
Local hypersensitivity reaction	0	31 (3.3)	0
Anaphylaxis	0	8 (0.9)	0
Hyperglycemia	7 (12.1)	35 (3.7)	5 (16.7)
Transaminases increased	6 (10.3)	33 (3.5)	3 (10.0)
Thrombosis	1 (1.7)	20 (2.1)	0
Hemorrhage	0	9 (1.0)	0
Embolism	0	0	1 (3.3)
Pancreatitis	1 (1.7)	37 (3.9)	2 (6.7)

While no deaths occurred in studies AALL07P2 and 100EUSA12, there were fatal AEs reported in the EMTP. There were 18 deaths reported in EMTP, 50% included disease progress as an adverse event leading to death, 7/18 included sepsis or infection as an event, and two patients had a stroke.

Serious adverse events were reported for 32.8% of study AALL07P2, 29.9% of study EMTP and 50% of study 1200 EUSA12. Events are tabulated below.

Table 12. Serious Adverse Events from Studies AALL07P2, 100EUSA12 and EMTP

Preferred Term	Study AALL07P2 N = 58 n (%)	Study EMTP N = 940 n (%)	Study 100EUSA12 N = 30 n (%)
Hypersensitivity	6 (10.3)	91 (9.7)	4 (13.3)
Febrile neutropenia	4 (6.9)	20 (2.1)	4 (13.3)
Neutropenia	5 (8.6)	13 (1.4)	0
Pancreatitis	0	31 (3.3)	2 (6.7)
Sepsis	3 (5.2)	10 (1.1)	1 (3.3)
Pyrexia	0	33 (3.5)	1 (3.3)
Hyperglycemia	0	32 (3.4)	0
Vomiting	2 (3.4)	21 (2.2)	1 (3.3)
Nausea	1 (1.7)	13 (1.4)	1 (3.3)
Urticaria	0	7 (0.7)	1 (3.3)
Pain in extremity	0	3 (0.3)	1 (3.3)
Stomatitis	0	0	1 (3.3)
Bacteraemia	0	1 (0.1)	1 (3.3)
Transient ischaemic attack	0	0	1 (3.3)
Sinus tachycardia	0	0	1 (3.3)
Skin ulcer	0	0	1 (3.3)
Lymphadenitis	0	0	1 (3.3)
Reversible posterior leukoencephalopathy syndrome	0	0	1 (3.3)
Alanine aminotransferase increased	0	25 (2.7)	0
Abdominal pain	1 (1.7)	10 (1.1)	0
Platelet disorder	1 (1.7)	1 (0.1)	0
White blood cell disorder	1 (1.7)	1 (0.1)	0
Hyperbilirubinaemia	1 (1.7)	3 (0.3)	0
Aspartate aminotransferase increased	0	15 (1.6)	0
Disease progression	0	10 (1.1)	0
Diarrhoea	0	9 (1.0)	0
Infection	0	9 (1.0)	0
Lipase increased	0	9 (1.0)	0

Discontinuations occurred in 7% of study AALL07P2 because of Grade ≥2 allergy or hypersensitivity to Erwinia asparaginase. In Study EMTP, 13% (122 patients) discontinued due to adverse events of whom 79 (8.8%) discontinued because of an allergic reaction and 43 (4.8%) because of other AEs including altered conscious state (2 patients), and one patient each with abdominal pain, ammonia encephalopathy, febrile neutropenia, hyperbilirubinaemia, hyperglycaemia with or without hypertriglyceridaemia, increased amylase/lipase, neurological event, nausea/emesis/hyperammonaemia. In Study 100EUSA12, 12 of 30 (40%) patients discontinued treatment: most commonly due to hypersensitivity (30%), pancreatitis (7%), and urticaria (3%).

Safety from the literature of most relevance to the requested indication could be captured as follows:

- Erwinia asparaginase in patients with *E coli* asparaginase allergy
  - Vrooman 2010, found that of the 42 patients who switched from *E coli* asparaginase to Erwinia asparaginase because of allergy, 27 completed all 30 weeks of planned asparaginase treatment, 2 discontinued due to severe pancreatitis and a third had a treatment interruption due to mild pancreatitis, 14 also developed allergy to Erwinia asparaginase including 9 with a systemic reaction. One patient developed hyperglycaemia requiring insulin. There were no reports of thrombosis or bleeding.
  - In Gupta 2020[38], 260 patients switched to Erwinia asparaginase from *E coli* asparaginase. Of those, 51 discontinued due to local or systemic allergy (n=24), pancreatitis (n=5) and the remainder discontinued for other reasons.
- Safety with prolonged use was described in Tong 2014a[39] and b[40]. Tong 2014a[41] reported toxicity data from 22 paediatric patients who switched from PEG asparaginase to Erwinia asparaginase due to allergy or silent inactivation. Of the adverse event types reported, a greater proportion of patients in the Erwinia asparaginase group experienced hypertriglyceridaemia (22% vs 32%), and hypercholesterolaemia (9% vs 37%). While there were more grade 1 or 2 hyperammonaemia events in the PEG asparaginase group (51% vs 41%), more patients in the Erwinia asparaginase group experienced a Grade 3 or 4 pancreatitis event (0% vs 9%). Pancreatitis was reported more frequently in the Erwinia asparaginase group for Grade 1 or 2 (0% vs 5%), and for Grade 3 or 4 (5% vs 9%). Two patients from each group developed thrombosis. Central neurotoxicity, that included somnolence, seizures or posterior reversible encephalopathy syndrome was reported in 10% of the PEG asparaginase patients and 5% of the Erwinia asparaginase patients. None of these differences reached statistical significance and the numbers of patients contributing events in most of the groups was very small.
- Safety in adults was described from small groups in two retrospective audits. Horvat 2016[i] did not report hypersensitivity or known asparaginase safety events in 10 patients who switched from pegaspargase. Bigliardi 2015[42], in a comparative study of first line treatment with either Erwinia asparaginase (11 patients) or *E. coli* asparaginase (2 patients) reported thrombotic complications (18%), pancreatic toxicity (18%), hyperglycaemia (27%), transient hepatotoxicity (grade 2-3 in 6 patients and grade 4 in 1 patient).

[38] Gupta 2020 (n 30)

[39] Tong 2014a (n 21)

[40] Tong 2014b (n 14)

[41] Tong 2014a (n 21)

[42] Bigliardi S, Morselli M, Potenza L, Coluccio V, Maccaferri M, Paolini A, Colaci E, Fantuzzi V, Faglioni L, Soci F, Nasillo V, Messerotti A, Pedrazzi P, Marietta M, Luppi M, Forghieri F. Safety profile of Erwinia asparaginase treatment in adults with newly diagnosed acute lymphoblastic leukemia: a retrospective monocenter study. Leuk Lymphoma. 2015 Mar;56(3):770-3. doi: 10.3109/10428194.2014.933216. Epub 2014 Aug 4. PMID: 24991716.

Post-marketing safety information revealed similar events, some of which have received further consideration in the evaluation report.

- Hypersensitivity/Immunogenicity
- Coagulation disorders
- Pancreatitis
- Hyperglycaemia
- Hepatotoxicity
- Infections
- Hyperammonaemia
- Secondary malignancies
- Renal toxicity
- Osteonecrosis due to drug-drug interaction with glucocorticoids
- Serious skin reactions

The submission includes information from the part of the Global Safety Database available to the Sponsor. As of the March 2021 update, 3,164 adverse events from post-marketing sources were available.

Other (e.g. companion diagnostic considerations, drug delivery device)

Therapeutic drug monitoring has been suggested by the Sponsor in the PI. The draft PI recommends changing from IV to IM dosing if desired levels of NSAA are not achieved. The optimal threshold is unclear. The SmPC mentions thresholds of both 0.4 IU/mL and 0.1 IU/mL.

Inter- and intra-individual variability, an apparent relationship between NSAA and asparagine levels, the actual surrogate for clinical efficacy and evidence of dose related toxicity together with the possibility of hypersensitivity also causing inactivation of Erwinia asparaginase, all point to a role for therapeutic drug monitoring.

The Sponsor explained the role of therapeutic drug monitoring to detect inadequate NSAA concentrations for efficacy or to detect silent inactivation in the case of pegylated asparaginase use but has not offered an opinion regarding the optimal sampling schedule or specific action based on the testing results for Crisantaspase . The Sponsor and has referred to local guidelines (e.g. ANZCHOG) to inform this aspect of care.

Therapeutic drug monitoring is performed in three Australian laboratories (The Children's Hospital Westmead, Royal Brisbane and Women's Hospital and the Alfred Hospital) but the performance of their assays compared with the assays used in the clinical studies and compared with one another is uncertain.

Real world evidence/real world data were included in the submission and are described throughout in the PK and safety sections of this document.

Risk management plan

The RMP evaluation was conducted over three rounds, after which there are some outstanding matters for consideration in the decision phase.

The Evaluator has reviewed EU-RMP version 1.1 (dated 10 February 2021; DLP 30 April 2020) and ASA version 1.0 (dated 14 April 2021) from the initial documents lodged, ASA version 1.1 (dated 25 March 2022) submitted with the response to the Round 1 report, and ASA version 1.2 (dated 3 March 2023) related to EU-RMP version 1.1 (dated 10 February 2021; DLP 30 April 2020).

After negotiation the Evaluator was satisfied with the summary of safety concerns outlined in the table below:

Table 13. Summary of safety concerns

The following Important Identified Risks have been added: • Hypersensitivity reactions • Pancreatic disorders (including hyperglycaemia) • Coagulation disorders • Hepatotoxicity • Posterior reversible encephalopathy syndrome (PRES) • Interaction with glucocorticoids • Infections • Hyperammonaemia • The following risk have not been added: • Renal impairment • Osteonecrosis secondary to an interaction with glucocorticoids
The following Important Potential Risk has been added: • Secondary Malignancy The following has not been added: • Interactions with methotrexate, cytarabine, vincristine, imatinib
The following Missing Information has not been added: • Use in the elderly • Use in infants aged less than one year • Use in pregnancy

The Sponsor has not agreed to inclusion of the medicine in the Black Triangle scheme. The RMP Evaluator has referred the matter for the consideration of the Delegate.

The Delegate agrees with the risk management plan (RMP) Evaluator that ERWINASE warrants inclusion in the Black Triangle scheme. ERWINASE is a new prescription medicine in Australia, therefore, as stated in the guidance on the TGA website, it is included in the scheme.

If approved, a condition of registration will be imposed requiring inclusion of the medicine in the Black Triangle Scheme. The Sponsor will be required to amend the PI and CMI accordingly prior to approval.

The Delegate proposes to accept all the recommended conditions of registration suggested by the RMP Evaluator.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Asparaginases have formed a component therapy for patients with ALL for over 4 decades, but they are immunogenic and can induce hypersensitivity reactions or silent inactivation.

ERWINASE is proposed as a substitution therapy, intended only for patients with ALL receiving E coli asparaginase as part of a multicomponent treatment protocol who have developed hypersensitivity.

The scientific rationale for another source of bacteria derived asparaginase is that Crisantaspase is manufactured using a plant bacterium. Patients are unlikely to have been systemically exposed to the bacteria Erwinia chrysanthemi and are therefore unlikely to have developed native antibodies prior to the commencement of treatment.

This submission relies on the PK endpoints (NSAA levels) as the main evidence to support use. An acceptance of this approach would be consistent with the international regulatory approach to evidence supporting Crisantaspase s. The SAA is a surrogate for asparagine (and glutamine) level, relevant because leukemia cells are dependent on asparagine. Reduction in asparagine and therefore the asparaginase activity is linked to anti-leukemic efficacy.

The proposed dose is based on equivalence to the dose of pegaspargase for which it is to be substituted. Six doses of Crisantaspase are needed to replace one dose of pegaspargase.

The submission proposes IV and IM dosing of 25,000 IU/m^2, dosed on Monday, Wednesday, and Friday to allow for weekends free from treatment. The dosing interval between Friday and Monday is around 72 hours. Using the trough NSAA threshold of 0.1 IU/mL the study 100EUSA12 of IV dosing found the NSAA level of 72 hours was reached in as few as 31% of patients. In the AALL07P2, with IM dosing, the lower bound of the 95% CI for the proportion of patients reaching the NSAA trough 0.1 IU/mL was 77% (point estimate 100%). NSAA is the surrogate endpoint for efficacy. The Delegate is concerned IV dosing does not reach conventional thresholds for acceptable activity with the proposed Monday/Wednesday/Friday dosing regimen in the majority of patients. Subject to the advice of the Advisory Committee on Medicines (ACM) the Delegate is not proposing to approve IV dosing for Crisantaspase .

The Sponsor proposes routine monitoring for NSAA levels in the dosing instructions for the PI but does not propose a monitoring regimen. Testing at 72 hours post last dose would appear informative, and based on the results from study 100EUSA12, testing during the second or subsequent courses may also be informative. The Sponsor has not proposed any instructions regarding how to schedule the routine testing. Presumably, this will be in accordance with local treatment guidelines and protocols, although the draft PI does not explicitly provide this instruction.

Dose adjustment is suggested in response to NSAA levels. Suggested increments, scheduling of repeat assessments is not included in the draft PI, and are difficult to ascertain from the submission documents.

Direct evidence of clinical efficacy of Crisantaspase for the proposed use is limited, and only one study used the proposed dose . In high-risk patients, completion of a course of asparaginase appears beneficial compared with missing doses. Whether all patients will benefit from switching is unclear. The Delegate recognises the decades of clinical use of Crisantaspase and has taken this into consideration when assessing the adequacy of the evidence supporting efficacy.

Interpretation of safety data from a safety data set that is set primarily in literature has challenges, because of incomplete or targeted nature of the safety reporting. Within those limitations, safety was reasonable well covered in the submission.

Safety differences between the asparaginase types were demonstrated in some studies. For example, in Tong 2014a hyperammonaemia was more frequent in the switched group (to Erwinia asparaginase). This is thought to be related to the greater glutaminase activity of Erwinia asparaginase, which was demonstrated in Tong 2014b .

Adolescent and young adult patients were more likely to experience an asparaginase related toxicity compared with younger patients. There are limited data in patients older than the young adult age range.

Hypersensitivity has been reported in patients switching to Erwinia asparaginase, including in the setting of the proposed indication for Australia – to Erwinia asparaginase from pegaspargase. Proportions of patients vary between studies but somewhere in the order of 10% of patients may be affected, and clear warnings in the PI are warranted. Hypersensitivity is potentially fatal, and the Sponsor proposes a contraindication to use in patient who have previously experienced a hypersensitivity event to Erwinia Crisantaspase .

Coagulation disorders, possibly as a consequence of impairment of hepatic synthesis of a range of asparaginase-dependent proteins can manifest as thrombotic or haemorrhagic disorders. In the clinical studies in the submission thrombosis occurred at a frequency of 2 – 3%, but in a meta-analysis of 1752 children the proportion of events was around 5% in patients receiving an asparaginase . Thrombotic events included CNS thrombosis (central venous thrombosis, central infarction/stroke, and with similar frequency to non-CNS events (mostly DVT)). Central thrombotic events have also been reported in adults during induction therapy with a regimen containing E coli asparaginase. Spontaneous adverse events reports reported in the PBRER, include similar events however unspecified asparaginase was the suspected medication. Without further clarification, the index of suspicion will need to remain high for such events with ERWINASE. The coagulation disorders also include an increased bleeding risk, and fatal and sever bleeding events have been reported including cerebral haemorrhage. Serious thrombosis or haemorrhage with prior L-asparaginase therapy are proposed as contraindications to ERWINASE,

Pancreatitis is an important risk that was identified specifically for ERWINASE in the clinical trials. Pancreatitis is seen in literature and adverse event reports. Fatal events, haemorrhagic and necrotising pancreatitis and pancreatic pseudocyst have been reported.

The Sponsor proposes contraindications in patients with serious hypersensitivity reactions to ERWINASE, or serious pancreatitis, thrombosis, or haemorrhagic events with prior asparaginase therapy.

As noted by the Evaluator, asparaginase has been reported to decrease insulin production and insulin-receptor expression, and therefore to cause hyperglycaemia. Another explanation involves an increased exposure to corticosteroid due to a reduction in plasma protein production. Hyperglycaemia occurred in between 3 and 12% in the clinical studies.

Osteonecrosis was also associated with concomitant glucocorticoid use. A mouse model has suggested that asparaginase may potential this adverse effect. This event appears more prominent in patients older than 10 years, and of female sex .

Posterior reversible encephalopathy syndrome (PRES) often has non-specific neurological symptoms that can range from headache through degrees of altered consciousness, visual disturbances and seizures. On imaging there is vasogenic oedema in the posterior circulation territory. It has been associated with cytotoxic medications, infection/sepsis and autoimmune disorders. Three cases were reported among the clinical studies in the submission, and 14 cases were included in the global safety database. A precautionary statement is proposed for inclusion in the ERWINASE PI.

Hepatotoxicity, along with the dysfunction of protein synthesis elevations of liver enzymes have been reported, and more rarely microvascular steatosis. The reports of severe disease are with the use of E coli asparaginase and while fulminant liver disease was not seen in clinical trials, but the global safety database analysis identified 41 cases of hepatitis, hepatitis acute, fulminant or toxic, hepatic failure and other descriptors of hepatotoxicity. A precautionary statement is proposed for the ERWINASE PI and hepatic monitoring is advised, as is discontinuation in the event of severe events.

Sepsis and infection are recognised risks with asparaginases, potentially due to a reduction in circulating asparagine. In the three clinical studies infection/sepsis occurred in between 3% and 10% of patients. ERWINASE is proposed for use as part of a multimodal treatment regimen. Other medicines in the regimen are also expected to contribute to infection risk. A precautionary statement is proposed regarding immunosuppression and infection.

Deamination of free amino acids leads to the production of ammonia and α-ketoacids. Rapid or prolonged deamination of glutamine and asparagine could overwhelm liver mechanisms to convert them to urea. Tong 2014a routinely monitored for hyperammonaemia in patients receiving Erwinia asparaginase and found 41% with grades 1 or 2 but 9% Grade 3 or 4. Smaller proportions of hyperammonaemia are reported in other series, but it is not clear whether routine monitoring occurred in these studies. The Sponsor proposes to include specific mention of hyperammonaemia as a subheading of neurological disorders in the ERWINASE PI.

The nonclinical evaluation did not include carcinogenicity studies, therefore clinical data are important to assess the risk. Secondary malignancies have been reported among ALL survivors, including haematological malignancies (AML, MDS, lymphomas). The attributable risk from asparaginase in patients who have received multiagent therapy is unknown.

Some patient populations are poorly represented in the submission, particularly those aged ≥65 years and paediatric patients aged < 1 year. Patients in the older aged groups may not be offered regimens that include asparaginases, and the indication is specifically as a substitution in a regimen that already includes pegaspargase. There is some mitigation of the uncertainty because of this limitation of the indication.

Conclusions

Erwinia asparaginase has been available internationally for decades, has been accessible through the Special Access Scheme in Australia and appears in the Australian eviQ cancer treatment guidelines.

As is often the case with literature-based submissions or mixed submissions, the data are old and have limitations. Decades of use have established a place for Crisantaspase s in the management of patients with hypersensitivity responses (overt or silent) to E coli derived asparaginases. Regardless of the history of use, the Sponsor must have satisfactorily established

the quality, safety, and efficacy of the medicine for the proposed use in this submission. There are limitations to the evidence presented. Important uncertainties in the submission are the optimal dosing regimen, optimising the use of therapeutic drug monitoring, and safety in adults.

Subject to satisfactory responses to the Delegate's questions, and to the advice of the ACM, at this preliminary stage the Sponsor's approach is potentially acceptable for IM dosing.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Crisantaspase is a made in a biological system. Are there any concerns with the reliance placed on literature to support the pharmacokinetics, efficacy and safety of Crisantaspase as a general approach?***

The ACM noted that there is considerable literature on the pharmacokinetics (PK)/ pharmacodynamics (PD), efficacy and safety of ERWINASE (Crisantaspase), however, there is significant variability in the quality of this literature.

The ACM noted that there is good supportive evidence of efficacy of *E.coli* derived asparaginase. However, the ACM expressed some concern that the PK/PD therapeutic effect and toxicity relationship is not scientifically established and therefore neither is the dosing schedule (including dose, interval and duration), the therapeutic target of the PD measure of enzyme activity or the therapeutic effect of non-completion of the full course. The ACM agreed that this is often common to medicines with a long history which have been established through precedent and consensus, especially in populations such as paediatrics.

The ACM considered the long history of use of asparaginase and its importance in the ALL protocols and was satisfied with the reliance placed on literature in this instance.

2. ***Please advise regarding the role of therapeutic drug monitoring of NSAA levels. Is there sufficient evidence to support a single threshold level for efficacy? If so, should it be 0.1 IU/mL or 0.4 IU/mL?***

The ACM agreed that the internationally accepted asparaginase activity threshold for sufficient asparagine depletion is ≥ 0.1 IU/mL. Clinical trials have also recommended this threshold and it is currently used in clinical practice.

3. ***If approved, the sponsor seeks intravenous (IV) and intramuscular dosing. Has sufficient evidence been provided to support the use of IV three times weekly dosing, given the low proportion of patients achieving a 72-hour NSAA of 0.1 IU/mL and no patients achieving a NSAA of 0.4 IU/mL in study 100EUSA12?***

The ACM noted studies comparing IM versus IV Erwinia asparaginase demonstrate a longer duration of effect with IM based on nadir of serum asparaginase activity (NSAA). It is generally demonstrated this is due to the slow absorption and distribution phase prolonging the effective duration of action.

The ACM noted protocols worldwide have allowed IV Erwinia asparaginase at 48 hourly dosing and IM dosing Monday, Wednesday, Friday. The mode and frequency of dosing is at the discretion of the individual centres and is generally based on what is reasonable and feasible for both the centre and the patient along with therapeutic drug monitoring.

The ACM was of the view that allowing both IV and IM dosing is beneficial and is in line with the approach already in use in clinical trials and treatment centres. For the paediatric population the use of IV dosing avoids multiple large injections into small muscles.

On balance the ACM advised that IV dosing (48-hours and 72-hours) should be available however noted that 72-hour dosing may not always achieve the desired NSAA levels/duration of effect. As such, the ACM recommended the scope of IV dosing should allow for clinical practice to determine the dosing regimen based on practicality and therapeutic drug monitoring.

4. ***Therapeutic drug monitoring is proposed using currently available testing. Are there limitations to access to testing that would make the sponsor's proposal infeasible for prescribers?***

The ACM advised that there is a NATA accredited lab that has this test available in almost every state in Australia and therapeutic drug monitoring is being performed increasingly more often. Limitations to access are slowly resolving over time. Available testing is able to cover most of the population and send away testing to an alternative laboratory is provided for those that cannot do testing on site. The ACM noted that the turnaround time is a little longer when send away testing is used but there is sufficient testing available.

5. ***The efficacy studies include paediatric patients, adolescents and young adults, and it is noted the eviQ guidelines caution against the use of asparaginase for patients over the age of 40 years. Have sufficient data been provided to support the use of this medicine in the remainder of the adult population with acute lymphoblastic leukemia?***

The ACM acknowledged asparaginase is a critical component of curative therapy for ALL and has been used regularly in adults. However, noted it should not be used in those with previous anaphylaxis or severe hypersensitivity to asparaginase formulations, severe hepatic impairment, existing or a history of pancreatitis, or previous haemorrhagic or severe thrombotic events.

The ACM considered eviQ guidelines which state PEG asparaginase should be used with caution in patients over 40 years of age and those with a body mass index (BMI) greater than 30 due to an increased risk of side effects. The ACM noted that some international literature provides recommendations as to what can be done in this patient population to mitigate the risk of side effects including closer monitoring. It is expected that more advice will come based on clinical trials in adults.

The ACM advised paediatric derived protocols to have been adopted for adults and have demonstrated a good response to therapy with patients achieving remission. ERWINASE is the only drug currently available for adult patients should they have a reaction to PEG asparaginase. The ACM support use in the adult ALL population noting that omission of asparaginase or insufficient depletions of asparagine increases the risk of relapse to patients which has a significant impact on patient care.

6. ***Other advice***

The ACM noted that the CMI wording 'your doctor will review your medicines and will ensure that ERWINASE will not be mixed with other medicines before being administered' should be reworded or removed. The ACM was of the view that this wording is vague and could cause confusion as ERWINASE is always given concurrently with prednisolone, vincristine and daunorubicin during induction.

The ACM noted that the CMI wording 'the amount you receive can change and will depend on the amount of asparaginase (the active substance in this medicine) in your blood, which can be checked during your treatment' should be amended. Assuming therapeutic dose monitoring is performed the amount of asparaginase the patient receives in any given dose will not be changed. Treatment may be stopped or given more frequently, assuming no antibody formation,

but the actual dose itself will not change. The ACM indicated this section of the CMI could state 'asparaginase activity in the blood may be monitored by a blood test'.

The ACM also noted that CMI wording 'your treatment will normally be given without interruption. If the treatment needs to be stopped, it can be started again at a lower dose' could alternatively state 'your treatment will normally be given without interruption, but for various reasons may need to be stopped'. The ACM advised that if asparaginase is stopped it is not started again at a lower dose and the inclusion of this statement in the CMI could be misleading.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

ERWINASE is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to pegylated asparaginase obtained from E. coli.

Outcome

Based on a review of quality, safety, and efficacy, and taking into account the deliberations of the ACM, the TGA decided to register ERWINASE for the following indication:

> *ERWINASE is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to pegylated asparaginase obtained from E. coli.*

Product Information

The Product Information approved with this submission for ERWINASE which is referred to in this AusPAR (and can be accessed on this AusPAR's webpage) may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #