EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2015
EMA/826135/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Oncaspar

International non-proprietary name: pegaspargase

Procedure No. EMEA/H/C/003789/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

6-MP	6-Mercaptopurine
Ab	Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute Lymphoblastic Leukaemia
ALT	Alanine Amino Transferase
AML	Acute Myeloid Leukemia
ANLL	Acute Non-Lhymphoblastic Leukaemia
API	Active Pharmaceutical Ingredient
Ara-C	Cytosine Arabinoside
AS	Asparagine Synthetase
ASNase	Asparaginase
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
AUL	Acute Undifferentiated Leukaemia
BFM	Berlin-Frankfurt-Münster
Bid	Bis in die
BMT	Bone Marrow Transplantation
BUN	Blood Urea Nitrogen
BW	Body Weight
CALLA+	Reactive to common ALL antigen
CCR	Continuous Complete remission
CHOP	Cyclophosphamide adriamycin, vincristine, prednisone
CIOMS	Council for International Organizations of Medical Sciences
CL	Total Clearance
CL/F	Total Clearance for extravascular administration
CMED	Cyclophosphamide, methotrexate, etoposide, decadron
CML	Chronic Myelogenous Leukemia
CNS	Central Nervous System
CON	Consolidation
CR	Complete remission
CSF	Cerebrospinal Fluid
CT	Computed chromography
CTC	Common Toxicity Criteria
CTD	Common Technical Document
CTEP	Cancer Therapy Evaluation Program
d	Day
DDP	Cisplatin
DI	Delayed Intensification
DIC	Disseminated Intravascular Coagulation
E. coli	Escherichia Coli
EEG	Electroencephalogram
EFS	Event Free Survival
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Unit
F	Female
F	Absolute Bioavailability
FAB	French–American–British classification

FDA	Food and Drug Administration
FL	Fluorescent (detection)
FSR	Final Study Report
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GOT	see AST
h	Hour
Hb	Haemoglobin
HD	High Dose
HI	Haematologic Improvement
HLA	Human Leukocyte Antigen
HPLC	High Performance Liquid Chromatography
HR	High Risk
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
IC50	Half Maximal Inhibitory Concentration
Im	Intensification Maintenance
IM	intramuscular
IND	Induction
INN	International Nonproprietary Names
INR	International Normalised Ratio
IPII	Increased Intensity Post-Induction intensification
ISS	Integarted Summary of Safety
IT	Intratecal
ITT	Intention To Treat
IU	International Unit
IU	International Unit
IV	intravenous
KDa	Kilo Dalton
Km	Michaelis-Menten constant
L-asp	L-asparaginase
LD50	Dose causing 50% Lethality
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LE	Leukaemic Event
LFS	Leukaemia Free Survival
M	Male
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MDH	Malic dehydrogenase
MDR	Multi Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
MIME	Methilgag, ifosfamide, methotrexate, etoposide
MR	Minor Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Image
MS/MS	Tandem Mass Spectrometry
MTD	Maximum Tolerated Dose
MTX	Methotrexate

NADH	Nicotinamide Adenine Dinucleotide
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOEL	No Observed Effect Level
NR	No Response
OAP-Bleo	Vincristine, cytarabine, prednisone, bleomycin
ORR	Overall Response Rate
OS	Overall survival
p.o.	Per os
PBS	Phosphate Buffer Saline
PD	Pharmacodynamic
PEG	Polyethylene Glycol
PEG-L-asp	PEG-L-asparaginase
PI	Patient Information
PII	Post-Induction Intensification
PK	Pharmacokinetics
POG	Pediatric Oncology Group
PR	Partial Response
PRD	Progressive Disease
PSUR	Periodic Safety Update Report
PT	Prothrombine Time
Pts	Patients
PTT	Partial Thromboplastin Time
q	Every (quaue)
qd	Every day (quaque die)
RER	Rapid Early Responders
RES	Reticuloendothelial System
RPLS	Reversible Posterior Leukoencephalopathy Syndrom
S. typhimurium	Salmonella typhimurium
s.c.	Subcutaneous
SD	Stable Disease
SE	Standard Error
SEM	Standard Error of Mean
SER	Slow Early Responders
sGOT	Serum Glutamate Oxaloacetate Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SOC	System Organ Classification
SPII	Standard Intensity Post-Induction intensification
SR	Standard Risk
STD	Standard Deviation
t1/2	Apparent elimination half-life
TE	Therapeutic Effect
TEAE	Treatment Emergent Adverse Event
TH	Transient hyperglycaemia
US	United States
VCR	Vincristine
VLDL	Very Low Density Lipoprotein
VP-16	Etoposide
Vss	Volume of distribution at steady state
Vz	Terminal Volume of distribution

WBC	White Blood Cells
WHO	World Health Organization
wk	Week
XRT	Radiation therapy
y o Yr	Year

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxalta Innovations GmbH submitted on 27 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Oncaspar, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in children, adolescents and adult patients.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that pegaspargase was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 January 2013. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Oncaspar has been given a Marketing Authorisation in the following countries:

Germany on 7 November 1994

Poland on 10 December 2008

United States on 1 February 1994

Kazakhstan on 15 November 2005

Russian Federation on 6 February 2001

Ukraine on 1 August 2005

Belarus on 1 July 2005

Argentina on 6 October 2004

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 27 June 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 October 2014.
- PRAC RMP Advice and assessment overview as adopted by PRAC on 6 November 2014.
- During a meeting of a Biologics Working Party on 17 November 2014, experts were convened to address questions raised by the CHMP.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- On 16th of January 2015, the Applicant requested a clock-stop extension of 3 months, which was granted by the CHMP on 22 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 July 2015.
- PRAC RMP Advice and assessment overview as adopted by PRAC on 9 July 2015.
- The Rapporteurs circulated an updated Joint Assessment Report to all CHMP members on 17 July 2015.
- On 22 July 2015, the Applicant requested a clock-stop extension of 3 months, which was granted by the CHMP on the 23rd of July 2015.
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues on 5 November 2015.
- PRAC Advice and assessment overview as adopted by PRAC on 6 November 2015.
- During a written procedure on 26 November 2015 the CHMP, in the light of the overall data

submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Oncaspar.

• The CHMP adopted a report on similarity of Oncaspar with Atriance, Evoltra, Iclusig, Sprycel, Xaluprine and Blincyto on 26 November 2015.

2. Scientific discussion

2.1. Introduction

Problem statement

Acute lymphoblastic leukaemia (ALL) is a heterogeneous group of lymphoid neoplasms that result from monoclonal proliferation and accumulation of lymphoblasts in the bone marrow, peripheral blood and other organs.

ALL is the most commonly diagnosed cancer in children and represents 25% of cancer diagnoses among children younger than 15 years. In absolute terms, however, ALL is a very rare disease, even in children. Its incidence has a bimodal distribution with a sharp peak among children aged 2 to 3 years (>90 per million per year), with rates decreasing to 30 per million by age 8 years (NCI at the NIH: Childhood Acute Lymphoblastic Leukemia Treatment, March 2013). A second steady increase in the incidence of ALL begins at approximately 50 years of age, with a peak incidence of about 2 per 100,000. Overall, estimated incidence in the EU is 1.28 per 100,000 persons, corresponding to a total of approximately 5,600 new cases per year.

The recognised chromosomal abnormalities in ALL result in biological differences in the condition, and are important for prognosis and for therapeutic decisions. For example, Philadelphia chromosome positive (Ph+) ALL, which is caused by the translocation of the BCR and the ABL genes, is associated with a very poor prognosis.

ALL is divided into subtypes based on the presence of B- or T-cell lineage-specific differentiation antigens detected on the surface of leukaemic blast cells. Precursor B-cell ALL (including early pre-B and pre-B-cell ALL) is the most common (approximately 70% to 80%) subtype in both children and adults. Mature B-cell ALL (Burkitt's leukaemia / lymphoma) has been reported in 2% to 5% of children and adults. T-cell ALL has been diagnosed in 15% to 25% of paediatric and adult patients with ALL. It occurs more commonly in older adolescents and young adults than in young children, with an incidence of approximately 25% of all ALL in patients 16 to 21 years of age.

The treatment for ALL typically consists of a remission-induction phase, an intensification (or consolidation) phase and continuation / maintenance therapy to eliminate residual disease. Treatment is also directed to the Central Nervous System (CNS) early in the clinical course to prevent relapse attributable to leukaemic cells sequestered in this site (Pui et al, 2008).

Treatment depends on the use of intensive multi-agent chemotherapy given over 6 to 9 months in combination with central nervous system prophylactic therapy with cranial radiation and intrathecal chemotherapy followed by maintenance chemotherapy for 2 to 3 years.

All phases of treatment involve combination chemotherapy. Current treatment guidelines (European LeukemiaNet and National Comprehensive Cancer Network) recommend treatment with Tyrosine Kinase Inhibitors (TKIs). In Europe, the following TKIs are currently approved for the treatment of ALL and LBL: Glivec (imatinib); Sprycel (dasatinib); Tasigna (nilotinib); Iclusig (ponatinib).

In addition, drugs used during induction typically include vincristine, prednisone, cyclophosphamide, doxorubicin and L-asparaginase. Cytarabine and methotrexate are often added during consolidation / intensification. Maintenance therapy frequently includes 6-mercaptopurine, methotrexate, steroids and vincristine (NCCN guideline, November 2015).

Allogeneic blood stem cell transplantation is of great importance especially in patients at high risk or after a recurrence.

All these protocols involve the use of L-asparaginase during induction and consolidation /intensification phases. The objective of asparaginase therapy is to deplete physiological asparagine so that it is unavailable to tumour cells.

Historically, native E coli-derived asparaginase was used as the initial intervention. However, treatment-limiting immune response can occur. Once hypersensitivity is apparent, it is necessary to switch to a different asparaginase preparation. Therapy can then continue until a treatment-limiting immune response to the substituted asparaginase occurs.

Pegaspargase (Oncaspar, Enzon Pharmaceuticals, Inc) was authorised in the US on 24 July 2006 for the first-line treatment of patients with acute lymphoblastic leukemia (ALL) as a component of a multi-agent chemotherapy regimen. Oncaspar was previously approved in the US in February 1994 for the treatment of patients with ALL who were hypersensitive to native forms of L-asparaginase. In Europe, Oncaspar was authorised in 1994 in Germany and in Poland in 2008 for the treatment of patients with ALL who were hypersensitive to native forms of asparaginase. The national marketing authorisations in Germany and Poland will be withdrawn upon launch of the centrally-authorised product Oncaspar.

Excellent progress has been made in the therapy of childhood ALL over the past five decades with combination chemotherapy and central nervous system (CNS) prophylaxis having improved the cure rate from 5% in 1950 to 85% in 2000 (Bailey et al, 2008). In contrast, while dose-intense multi-agent regimens administered to adult patients with ALL now achieve remission rates exceeding 80%, 5-year survival is only around 40% (Faderl et al, 2008).

About the product

Oncaspar is a modified version of the enzyme L-asparaginase. The International Non-proprietary Name (INN) is pegaspargase. The chemical name is monomethoxypolyethylene glycol succinimidyl L-asparaginase. Asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG; molecular weight of 5,000) to the enzyme, forming the active ingredient pegaspargase.

The mechanism of action of L-asparaginase is the enzymatic cleavage of the amino acid L-asparagine into aspartic acid and ammonia. Depletion of L-asparagine in blood serum results in inhibition of protein-synthesis, DNA-synthesis and RNA-synthesis, especially in leukaemic blasts which are not able to synthetise L-asparagine, thus undergoing apoptosis.

Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid withdrawal during treatment with the enzyme L-asparaginase. The PEGylation does not change the enzymatic properties of L-asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme (see SmPC section 5.1).

The applied indication was as follows:

“Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in children, adolescents and adult patients”.

The recommended indication is as follows:

Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients (see SmPC section 4.1)

Oncaspar should be prescribed and administered by physicians and health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available.

Oncaspar is usually employed as part of combination chemotherapy protocols with other antineoplastic agents (see also section 4.5).

The recommended dose of Oncaspar in patients (including children) with a body surface area ≥ 0.6 m^2 and who are ≤ 21 years of age is 2500 U (equivalent to 3.3 ml Oncaspar)/m^2 body surface area every 14 days. Children with a body surface area <0.6 m^2 should receive 82.5 U (equivalent to 0.1 ml Oncaspar)/kg body weight every 14 days.

For adults >21 years, unless otherwise prescribed, the recommended posology is 2000 U/m^2 every 14 days (see SmPC section 4.2).

Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of Oncaspar. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section 4.4).

Oncaspar can be given by intramuscular injection or intravenous infusion. For smaller volumes of Oncaspar, the preferred route of administration is intramuscular. When Oncaspar is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If higher volume is given, the dose should be divided and given at several injection sites. Intravenous infusion of Oncaspar is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% dextrose solution together with an already-running infusion (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

Oncaspar solution for injection or infusion is a sterile, preservative-free, isotonic, single-dose solution of PEGylated L-asparaginase (INN: pegaspargase) in phosphate buffered saline intended for intramuscular injection or intravenous infusion. The product is proposed as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in children, adolescents and adult patients.

2.2.2. Active Substance

A) Asparaginase

General information

Asparaginase is a homotetrameric enzyme, comprised of four identical subunits with a mass of 34,592 kDa coupled by weak, non-covalent, largely hydrophobic interactions. The tetrameric structure of the L-asparaginase enzyme is required for enzymatic activity. The asparaginase used for production of Oncaspar is a high-affinity type II asparaginase expressed in *E. coli*.

Manufacture, characterisation and process controls

The manufacturing process starts with the thawing of the *E. Coli* working cell bank. The cells are expanded in shake flask prior transfer into seed and production bioreactor with appropriated controls which includes pH, dissolved oxygen and temperature.

When the harvest criteria is achieved, the cells are harvested, homogenized and cell debris is separated prior to further purification. The different steps in purification includes hydrophobic interaction chromatography, anion and cation exchange chromatography as well as clearance steps to effectively deplete product and process related impurities. Following purification the active substance is dispended into sterile container and subjected to testing and release.

The characterisation and testing of banked cell substrates were performed in accordance with ICH Q5D. Raw materials are tested according to European pharmacopoeia (where available), or according to in-house monographs.

Process validation

Process validation consisted in the analysis of data derived from three consecutive full-scale lots of asparaginase. Evaluation of in-process controls, analytical control of buffers, and release quality controls demonstrate that the manufacturing process of asparaginase is consistent. Removal of key impurities throughout the process was satisfactorily addressed at each step. The stability of process intermediates and buffers was appropriately evaluated. The lifetime of columns was evaluated.

Characterisation

Orthogonal methods have been applied to determine and confirm the expected primary structure of asparaginase, physicochemical properties and purity of asparaginase. This includes overall amino acid sequence, N-terminal sequence, disulphide bond configuration, molecular mass and isoelectric point as well as product and process related impurities. Furthermore biologic activity was determined by enzyme kinetics.

Specification

The proposed release tests are acceptable, including measures of enzymatic activity, and methods to control for product-related substances, product-related impurities and process-related impurities. During the procedure, some acceptance criteria were revised and the Applicant completed a review of all analytical procedure validation data, including results from original validation studies and subsequent analytical method transfers. As no international reference standard is available for asparaginase, the strength of the product is reported as product specific in-house units.

Stability

Data obtained from primary stability studies support the claimed shelf-life. The claimed holding time was also considered acceptable.

B) Pegaspargase active substance

The active substance pegaspargase (pegylated asparaginase) is a covalent conjugate of *E. coli*-derived asparaginase with monomethoxypropylene glycol. It results from the reaction between polyethylene glycol succinimidyl succinate (SS-PEG) and exposed primary amines on the asparaginase

Manufacture

The pegaspargase active substance manufacturing process starts with the pegylation reaction. Asparaginase is combined with polyethylene glycol succinimidyl succinate (SS-PEG) followed by clarification and purification steps. Finally the process solution is diluted to meet the final product specification of 750 U/mL. The active substance was subjected to testing and can be hold at 2-8°C prior to manufacturing of the final finished product.

For the active substance manufacturing process asparaginase and SS-PEG are used. A flow chart of the manufacturing process of SS-PEG, as well as its specification, have been provided. The potential/actual impurities were also discussed and justified from the toxicological point of view.

Other raw materials (including components of the final formulation) are tested according to European pharmacopoeia (where available), or according to in-house monographs.

Process validation

Process validation consisted in the analysis of data derived from three consecutive commercial lots of pegaspargase. All batches used asparaginase manufactured by the previous supplier M, which is not the proposed supplier L within the framework of this application. Considering that Supplier L and Supplier M products were demonstrated comparable, this approach can be considered acceptable. Evaluation of in-process controls, analytical control of buffers, and release quality controls demonstrate that the manufacturing process of pegaspargase is consistent.

Changes were introduced during development. Batch testing results and comparability exercises that were executed to support these changes indicate a high degree of similarity between the pre- and post-change product.

Characterisation

Characterisation studies have been provided for structure and properties relevant for the pegylated enzyme. They included analyses of the number and sites of pegylation, higher order structures, purity and impurities, and enzyme kinetics. Elucidation of primary structure was not repeated since it was already done at the level of asparaginase.

The secondary structure of the protein was determined by circular dichroism spectroscopic analysis of three L-ASNase conformance batches.

Characterisation studies were derived from two batches that were used in the comparability program between pegaspargase manufactured from Supplier L asparaginase *vs.* pegaspargase manufactured from Supplier M asparaginase. Product- and process-related impurities which can be present in the active substance pegaspargase have been identified. They are controlled at release, and during stability if appropriate. The un-pegylated asparaginase, which was classified as product-related substance, is monitored only by indirect methods.

Specification

The pegaspargase bulk solution (active substance) and the finished product manufacturing processes are continuous; thus, no formal batch release is performed at the active substance level. The proposed specification is a subset of the testing panel performed at the finished product batch release. All proposed acceptance criteria are identical, apart from potency which is slightly tighter.

Appropriate justification including clarification on the method used to calculate the acceptable ranges has been provided.

Stability

No formal shelf-life is claimed for the active substance and the claimed holding time before entering into the finished product manufacturing process was acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented in a vial (type I glass), with a fill volume of 5 mL, at the strength of 750 U/mL. The product is formulated in a buffer solution with sodium dihydrogen phosphate monohydrate/disodium phosphate heptahydrate and sodium chloride.

Pharmaceutical Development

The finished product was developed for parenteral administration in a phosphate buffered saline solution. Its formulation has remained unchanged since the start of product development. No overage is claimed however an overfill is applied to ensure an extractable volume of 5.0 mL.

In 2008 an alternative manufacturer was added and thereafter, became the sole manufacturing site for Oncaspar production. Compatibility of the container closure system with the dosage form was assessed with respect to stability testing, media fill testing and container closure integrity testing. The microbiological quality complies with European requirements for sterile products. The integrity of the container closure system is monitored by both a dye ingress test and a bacterial immersion test. The compatibility of the finished product with diluent solution (0.9 % NaCl; 5% glucose solution) and representative catheters was appropriately addressed.

Manufacture of the product and process controls

Overall the manufacturing process is well described and appropriately validated.

The manufacturing process can be summarised as follows: the filling equipment is steam sterilised, the bulk substance solution passes through a filter and is subsequently filled into vials and closed by a stopper. After capping and sealing vials are subjected to release testing including visual inspection and are transferred into 2-8°C for storage.

Product specification

The finished product specification includes tests for general attributes, enzymatic activity, identity, and purity. The proposed specification for the finished product is identical to the specification for Quality Control testing of the active substance, with the exception of three tests which are only performed on the finished product (extractable volume, sub-visible particles, sterility) and one test for which the acceptance criteria differ between the active substance and the finished product (potency).

The Applicant provided all the requested information and details in order to evaluate the appropriateness of the proposed specifications. Some of the acceptance criteria have been tightened if compared with the originally submitted ones. The specifications have to take into consideration that, using as starting material a SS-PEG containing a low level of impurities, a low and stable aggregates level is expected as demonstrated by the Applicant.

Stability of the product

The Applicant originally claimed a 1-year shelf life at 2-8°C but stability data clearly show that there is a purity decrease due to the release of free PEG from the pegylated molecule. Moreover the enzymatic activity of pegaspargase increases over the claimed shelf-life. This is of concerns since the instability of the product could lead to administrate lower dose of pegaspargase and significant amount of asparaginase at end-of shelf-life, with potential *in vivo* effects of release of PEG from asparaginase (*in vivo* half-life, immunogenicity). The Applicant accepted to revise the shelf-life from 12 months to 8 months in order to limit de-PEGylation. As a result, the increasing of enzymatic activity of pegaspargase over the new proposed shelf-life has been limited and the Applicant's proposal is endorsed. The potential impact in terms of efficacy and safety of the increasing of activity of pegaspargase over the new proposed shelf-life and related purity decrease is discussed in clinical assessment (see discussion on clinical pharmacology).

Adventitious agents

Oncaspar is manufactured from an L-ASNase expressed in *E. coli*, a bacterial cell host which does not support replication of viral agents which may infect humans. The manufacturing process (cells banks and production) involves materials of biological origin that have been fully and appropriately documented regarding the viral safety. The adventitious agent safety evaluation presented is sufficient and adequate.

Comparability exercise for finished product

Oncaspar was developed in the late 1980s and early 1990s. It was authorised in the US in 1994 in second line use in ALL following the development of hypersensitivity to native asparaginase: authorisation in the first-line treatment of ALL was obtained in 2006. This was based primarily on clinical data obtained in Study CCG-1962 and CCG-1991. Oncaspar was registered in Germany in 1994 and in Poland in 2008 for the treatment of patients with ALL who were hypersensitive to native forms of asparaginase.

The US and German products used asparaginase from different sources. Oncaspar sold in the US used enzyme manufactured by Supplier M. Oncaspar authorised in Germany and Poland used enzyme manufactured by Supplier K. In both cases the PEGylation and subsequent manufacturing steps were performed by Sigma-Tau Inc in its Indianapolis manufacturing facility.

In 2010 in US the enzyme manufacturer was switched from Supplier M to Supplier L in response to Supplier M discontinuing manufacture of asparaginase. The enzyme Master Cell Bank is a descendant of the Master Cell Bank used by Supplier M.

In Europe, no change to the manufacturer of enzyme active substance has ever been made–all Oncaspar distributed in Europe has been manufactured using asparaginase from Supplier K.

The Applicant strategy was to submit a MAA for a product containing the enzyme supplied by Supplier L on the basis that the active substance is comparable to the pegaspargase containing both Supplier M and K enzyme. To support the use of the Supplier L enzyme, the product was analytically compared with Supplier M asparaginase (to demonstrate comparability with the product used in all original development studies and commercially used in the USA for decades); and with Supplier K asparaginase (to demonstrate comparability with the product commercially used in the EU since 1994). Furthermore, the comparability studies between PEGylated Supplier L *vs.* PEGylated Supplier M asparaginase and between PEGylated Supplier L asparaginase *vs.* PEGylated Supplier K asparaginase were also performed at the finished product level.

Due to discontinuation of asparaginase production by Supplier M, only limited data were available for the comparison between Supplier M and Supplier L batches. Based on few data provided, it appears that Supplier L and Supplier M asparaginase/pegaspargase are comparable in terms of

primary and higher order structure, extent of modification with PEG, activity and stability behaviour. Higher purity results are observed for Supplier L batches, especially at the level of asparaginase. Low levels of 3 impurities, proven to be product-related compounds, were reported to be found in Supplier L asparaginase however were not present at measurable levels in Supplier M asparaginase. Comparability between Supplier L and Supplier K asparaginase/pegaspargase included three batches of each supplier. As for Supplier L *vs* Supplier M, K and Supplier L asparaginase/pegaspargase were found to be essentially similar with respect to structure, pegylation, activity and stability behaviour. A certain variability has been observed for enzyme kinetics parameters however it remains within the pre-defined acceptance criteria. The overall purity profile of Supplier L asparaginase appears to be higher than K asparaginase.

To enable a conclusion on comparability, further explanation was requested on the setting of acceptance criteria and the impact of using different PEG suppliers. The Applicant was also requested to perform a direct side-by-side comparison between release data for historical batches (Supplier M) and the batches produced using Supplier L asparaginase. The data range of lots of Supplier L asparaginase and lots of Supplier L-pegaspargase/finished product were compared to lots of Supplier M asparaginase and lots of Supplier M derived-pegaspargase/finished product. In addition, stability profiles of Oncaspar-Supplier M and Oncaspar-Supplier L were also assessed. Overall, data support the conclusion that both products derived from Supplier L and Supplier M asparaginase are comparable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance was of acceptable quality. The active substance and finished product manufacturing processes have been satisfactorily described and the validation data shows consistent manufacture.

Specification limits and analytical methods are suitable to control the quality of the active substance and finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The results indicate that the active substance as well as the finished product can be reproducibly manufactured and adequately controlled.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some additional points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme for Oncaspar is a battery of studies conducted in late 1980s-early 1990s in compliance with the standards of the day. These studies were also used to support the marketing authorisations in the USA (1994), Germany (1994) and Poland (2008). All non-clinical studies were carried out testing PEG-L-asparaginase manufactured using native enzyme produced by Supplier M, with the exception of a pharmacokinetic study in Rhesus monkeys where PEG-L-

asparaginase obtained from native enzyme produced by Supplier K (a source of Oncaspar-Medac) was also used.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of *in vivo* studies published in the literature were conducted in mice inoculated malignant cells or in dogs with lymphosarcoma. The summary of these studies is provided in the table below.

Table 1: Summary of primary pharmacodynamics studies

Study Reference	Species (Strain)	Dose (mg/kg) Route	Results	Batch
Abuchowski (1984) Not GLP	C3H/HeJ mice infected with 6C3HED lymphoma cells 5 mice/group	Vehicle Asparaginase: 25, 50, 100, 200, 250 IU/kg i.p. PEG-L-Asparaginase: 25, 50, 100, 125, 250 IU/kg i.p. Single dose Treatment begun one day post-infection	Control mice Animals died within 14 days. Asparaginase 25 – 200 IU/kg: all animals died. 250 IU/kg: all animals were cured (animals surviving 60 days were considered cured). PEG-L-Asparaginase 25 – 100 IU/kg: 1 or 2 animals/5 cured. 125 – 250 IU/kg: all animals were cured.	Not available
	BDF1 mice infected with L5178Y lymphosarcoma cells 5 mice/group	Vehicle Asparaginase: 250, 500, 1000 IU/kg i.p. PEG-L-Asparaginase: 250, 500, 1000 IU/kg i.p Single dose Treatment begun one day post-infection	Control mice Animals died within 21 days. Asparaginase 250 – 500 IU/kg: all animals died. 1000 IU/kg: 2 animals were cured. PEG-L-Asparaginase 3 or 4 animals were cured.	Not available
Study #6 (1983) GLP	C3H/HeJ mice infected with 6C3HED lymphoma cells 5 mice/group	Vehicle PEG-L-Asparaginase: 200, 400 IU/kg i.p. 400, 800, 1200 IU/kg i.m. Single dose Treatment begun one day post-infection	Control mice Animals died within 16 days. i.p. injection 4 and 5 were animals cured with 200 and 400 IU/kg respectively. i.m. injection 2, 2 and 4 animals were cured with 400, 800 and 1200 IU/kg respectively.	28
MacGrath (1982) Non GLP	Lymphosarcoma bearing dogs 12 dogs (9M + 3F) Age range: 3-12 y	The dogs received conventional chemotherapy and/or L-asparaginase before or after treatment with PEG-L-Asparaginase i.p. Diverse administration schedules: 15 – 200 IU single dose, weekly or every 2 weeks	9/12 responded to PEG-L-Asparaginase Duration of remission: 2 to 14 weeks and 7 months for one dog Induction or remission not dose-dependant Generally well tolerated (one dog had adverse reactions consisting in rear end weakness, ataxia, lethargy and loss of appetite)	28

Mac Ewen (1987) Non GLP	Spontaneous malignant lymphoma bearing dogs 37 cancer dogs (19 M + 18F) 4 normal dogs (2M + 2F)	Group 1: 20 dogs (11 M+ 9F, 8 received prior chemotherapy) PEG-L-Asparaginase i.p. 10 IU/kg (10 dogs) or 30 IU/kg (10 dogs) weekly Group 2 : 17 dogs (8 M+ 9F, none received prior chemotherapy) PEG-L-Asparaginase i.p. 30 IU/kg weekly for 2 weeks followed by combination chemotherapy: vincristine, cyclophosphamide, methotrexate, prednisone + PEG-L-asparaginase 30 IU/kg for 1 month Dogs of both groups received PEG-L-Asparaginase every 2 weeks during the duration, of remission Normal dogs: 200 IU/kg once a week for 2 weeks (2 via IV and 2 via i.m. route) and then 1200 IU/kg weekly for 2 weeks	Group 1: - 7 dogs (1 at 10 IU/kg and 6 at 30 IU/kg) had complete response (including 1 that received prior chemotherapy) - 7 dogs (5 at 10 IU/kg and 2 at 30 IU/kg) had partial response (including 3 that received prior chemotherapy) - Duration of the response: 14 -60 days for dogs that received prior chemotherapy and 14-102 days for dogs that did not receive prior chemotherapy Group 2 : - 13 dogs had complete response - 2 dogs has partial response - Duration of the response: 7 – 441 days - 4 dogs were on maintenance therapy from 16 to 28 months - Median remission time: 126 days Adverse reactions: Death due to tumor massive breakdown (2 dogs) Disseminated intravascular coagulation within 6 hours of treatment(1 dog) Vomitus shortly after injection(3 dogs) Soft stools 2 -3 days after treatment (3 dogs) Collapse immediately after 1st injection (1 dog) apparently related to an anaphylactic-type reaction Normal dogs No adverse effects except a mild inhibition of body weight gain when receiving 1200 IU/kg and increased transaminase (1 dog).	PASPE-1104 PAS-86B-1108 PAS-86C-1109 PAS-86K-1110

<table>
<tr>
<td>MacEwen (1992)
Non GLP</td>
<td>Lymphoma bearing dogs
69 (not previously treated) dogs (40 F + 29 M)</td>
<td>Group A: PEG-L-asparaginase given as part of a 6 cycle chemotherapy schedule, in combination with vincristine, cyclophosphamide and doxorubicin.
Group B: L-asparaginase given as part of a 6 cycle chemotherapy schedule, in combination with vincristine, cyclophosphamide and doxorubicin.
ncristine,cyclophosphamide and doxorubicin.</td>
<td>Results
<table>
<tr><td></td><td colspan="2">Chemotherapy + PEG-L-ASPARAGINASE</td><td colspan="2">Chemotherapy + L-ASPARAGINASE</td></tr>
<tr><td></td><td>NUMBER</td><td>(%)</td><td>NUMBER</td><td>(%)</td></tr>
<tr><td>TOTAL NUMBER OF DOGS</td><td>35</td><td></td><td>34</td><td></td></tr>
<tr><td>CR</td><td>30</td><td>(85.7)</td><td>32</td><td>(94)</td></tr>
<tr><td>PR</td><td>3</td><td>(8.6)</td><td>0</td><td></td></tr>
<tr><td>NR</td><td>2</td><td>(5.7)</td><td>2</td><td>(6)</td></tr>
<tr><td>MEDIAN REMISSION</td><td>217 days</td><td></td><td>214 days</td><td></td></tr>
<tr><td>MEDIAN SURVIVAL (RANGE)</td><td>356 days (19 – 1030)</td><td></td><td>319 days (25 – 1090)</td><td></td></tr>
</table>
Adverse reactions
GROUP A
Generalized urticarial reaction after repeated administration (1 dog)

GROUP B
Limb oedema at injection site (1 dog)
Anaphylactic shock, seizures (1 dog)</td>
<td>PASPE-1104
PAS-86B-1108
PAS-86C-1109
PAS-86K-1110</td>
</tr>
</table>

Secondary pharmacodynamic studies

No study aimed at predicting potential off-target effects of PEG-L-asp was submitted (see non-clinical discussion).

Safety pharmacology programme

No stand-alone safety pharmacology studies have been submitted by the Applicant. Safety pharmacology endpoints were integrated in the experimental design of the repeat-dose toxicity studies (See Repeat-dose toxicity) and a published study in lymphoma bearing dogs (Teske, 1990)

investigating L-Asparaginase at doses of 200, 800, 3000 IU/kg IV for a duration of 3 months did not show any effect on the general behavior and ECG.

Pharmacodynamic drug interactions

No dedicated study aimed to assess the PD drug interaction was performed.

Published information is available describing potential pharmacodynamic drug interactions of PEG-L-asparaginase with other drugs that are used for the treatment of tumours in different animal models.

The antitumour activity was studied in dogs suffering from spontaneously occurring malignant lymphoma. Twenty dogs were treated with either PEG-L-asparaginase (10-30 IU/kg i.p., weekly) alone or combined with one cycle of chemotherapy (vincristine, cyclophosphamide, methotrexate and prednisone), followed by maintenance therapy with PEG-L-asparaginase (30 IU/kg i.p., weekly; n=17 dogs). With the addition of chemotherapy agents, the response rate (complete and partial response) was 88% (15/17 dogs) versus 70% (14/20 dogs) for PEG-L-asparaginase alone when used as a single agent (MacEwen, 1987).

In MiaPaCa-2 tumour xenograft mouse model, a synergistic anti-tumour activity was noted when PEG-L-asparaginase was combined with gemcitabine. PEG-L-asparaginase and gemcitabine were administered alone or in combination. Observed tumour growth inhibition as compared to untreated controls was 59% for PEG-L-asparaginase alone, 64% for gemcitabine alone and 86% for the combination of both drugs. No increase in response was seen with increased doses of PEG-L-asparaginase.

2.3.3. Pharmacokinetics

Two non-GLP pharmacokinetics and pharmacodynamic studies (#04-2861 and #04-3082), and two GLP toxicology/toxicokinetic studies (Studies #824-015 and #824-016) were carried out comparing PEG-L-asparaginase with new PEG-L-asparaginase conjugates. No non-clinical study was conducted with the PEG-L-asparaginase derived from Supplier L supplier which is proposed for marketing.

Table 2: Summary of bioanalytical methods used in PK/TK studies

Species	Test Item	Year	Study code	Paper	L-asparaginase activity method reference
Mouse	PEG-L-asparaginase	1983	Study #7	Viau, 1986	Not available (presumably Jayaram, 1974)
Rat	PEG-L-asparaginase	1983	Study #3	Viau, 1986	Not available (presumably Jayaram, 1974)
Dog	PEG-L-asparaginase	1983	Studies #4a, #4b	Viau, 1986	Not available (presumably Jayaram, 1974)
Mouse	PEG-L-asparaginase L-asparaginase	1984	-	Abuchowski, 1984	Jayaram, 1974
Mouse	PEG-L-asparaginase L-asparaginase	1987	Study #53	-	Not available (presumably ENZON SOP ver 1)*
Rabbit	PEG-L-asparaginase L-asparaginase	Not applicable	-	Ho, 1988	Cooney,1970 modified according to Ho et al., 1988
Rat	PEG-L-asparaginase	2005	Study #04-2861	-	ENZON Method Appendix A of Appendix D of the study report
Dog	PEG-L-asparaginase	2006	Study #04-3082	-	ENZON Method Appendix A of Appendix F of the study report
Monkey	PEG-L-asparaginase	Not applicable	NIH study	Berg, 1993	Cooney, 1970 modified according to Berg, 1993
Rat	PEG-L-asparaginase	2007	Study #824-015	-	Method validation study report 06-8473
Dog	PEG-L-asparaginase	2007	Study #824-016	-	Method validation study report 06-8481

Absorption

In mice, PEG-L-asparaginase was found to have a greatly extended plasma half-life compared to native L-asparaginase, of 3.75 days versus 0.21 days and immunization with PEG-L-asparaginase had no effect on the clearance of the drug (Abuchowski, 1984). Systemic exposure was similar in mice receiving the test drug via i.p. or i.v. routes and slightly lower with i.m. administration. However the t1/2 was similar for all three routes of administration and asparaginase activity was still detectable up to 13 days after dosing (Study #7). In mice dosed via the i.m. route, plasma asparaginase activity was significantly longer for PEG-L-asparaginase compared to native L-asparaginase, 8 days versus less than 24 hours (Study #53).

In rats, following i.m. and i.v. administration of PEG-L-asparaginase, Cmax and AUC values increased with the increasing dose in a proportional fashion (Study #04-2861). Study #824-015 also supported that systemic exposure of rats increased with the increasing single dose: following a single i.v. administration of 100 and 500 IU/kg of PEG-L-asparaginase, plasma asparaginase activities were quantifiable up to 336 h post-dose except four female out of 8 given the low dose of 100 IU/kg PEG-L-asparaginase and one female out of 8 given the high dose of 500 IU/kg. Plasma asparaginase activities were also increased in the plasma of rats after multiple dosing (Study #3).

In rabbits, plasma L-asparaginase activity dropped rapidly after the administration of native L-asparaginase (t1/2 of 20h) being barely measurable on day 4 following the injection. Plasma asparagine concentration returned to normal by day 6 after dosing. With PEG-L-asparaginase, plasma L-asparaginase activity remained detectable till day 27 with a t1/2 of 144 h and plasma asparagine levels were depressed for 27 days (Ho, 1988).

In dogs, the i.m. bioavailability in dogs was around 100% independently by the administered dose. No dose-dependency of t1/2 or CL was observed after either i.v. or i.m. injection. Plasma asparagine concentration decreased to undetectable levels within 10 minutes following i.v. and i.m. administration of PEG-L-asparaginase. In the dogs treated with PEG-asparaginase i.m., asparagine did not recover until Day 17 and Day 23 for the mid-dose and low-dose group, respectively, while it was undetectable for the entire study (23 days) for the high-dose group (Study #04-3082). In another study (#824-016), following single intravenous administration of 100 and 500 IU/kg of PEG-L-asparaginase, plasma asparaginase activity was quantifiable for the entire 14-day sampling period except for one dog where activity was apparent through day 10 but not on day 14. The systemic exposure to asparaginase activity in males after intravenous administration of PEG-L-asparaginase was approximately equal (within ± 30%) to that in females after 100 IU/kg doses, while it was slightly greater than that in females after 500 IU/kg doses. Dog studies #4a and #4b found no major differences in plasma L-asparaginase levels which may be attributed to gender effect.

In monkeys, the pharmacokinetics of PEG-L-asparaginase produced using two different suppliers of native L-asparaginase, Supplier M and Supplier K showed no apparent differences in depletion of L-asparagine from the plasma and CSF, with plasma L-asparagine undetectable for at least 14-25 days after i.m. administration of PEG-L-asparaginase at the dose of 2,500 IU/m^2.

Table 3: Pharmacokinetic parameters from pharmacokinetics and toxicokinetic studies with PEG-L-asparaginase in rodents

Parameter	**Units**	**Abuchowski, 1984**		**Study #7**			**Study #53**	**Study #04-2861**						**Study #824-015**			
Species		BDF_1 mouse		Swiss-Webster mouse			Swiss-Webster mouse	Sprague-Dawley rat						Sprague-Dawley rat			
N/dose		12 (M)		15 (F)			12 (F)	5 (F)						8 (M and F)			
PK		CA		CA			CA	CA						NCA			
Route		i.p.	i.p.§	i.v.	i.p.	i.m.	i.m.	i.v.			i.m.			i.v.			
Dose	UI/kg	250	250	260	260	260	400	26	87	260	26	87	260	100 (F)	100 (M)	500 (F)	500 (M)
Dose	UI/m^2	750	750	780	780	780	1,200	156	522	1560	156	522	1560	600	600	3,000	3,000
Cmax	UI/mL	-	-	-	-	-	-	0.74	1.99	5.18	0.20	0.81	1.97	0.97	1.36	5.91	6.03
tmax	d	-	-	-	-	-	-	-	-	-	1.55	1.48	1.45	0.66	0.45	0.63	0.50
AUC_{last}	d*UI/mL	-	-	-	-	-	-	-	-	-	-	-	-	2244	3912	17280	17424
AUC_{INF}	d*UI/mL	-	-	42.70	40.07	32.54	36.85	1332	4464	12048	574	2472	7344	2952	4104	18672	18360
AUC/Dose	(d*UI/mL)/(UI/kg)	-	-	0.16	0.15	0.13	0.09	51.2	51.3	46.3	22.1	28.4	28.2	29.5	41.0	37.3	36.7
t1/2	d	3.75	3.50	2.23	2.38	2.22	3.05	2.31	2.74	2.80	1.97	2.36	3.30	3.31	2.84	3.23	3.12
Vss or Vz	mL/kg	-	-	-	-	-	-	39.3	44.6	50.6	-	-	-	97.60	63.4	83.30	77.60
CL	mL/d/kg	-	-	0.16	-	-	-	11.76	11.52	13.44	-	-	-	20.57	14.18	16.39	16.63
CL	mL/h/kg			0.01				0.49	0.48	0.56				0.86	0.59	0.68	0.69
Absolute availability	%	-	-	100	93.8	76.2	-	100	100	100	43.0	55.1	61.0	100	100	100	100

§ Immunised mice ; CA: compartmental analysis; NCA: non-compartmental analysis; M: male; F: Female.

Table 4: Pharmacokinetic parameters from pharmacokinetics and toxicokinetic studies with PEG-Lasparaginase in non-rodents

Parameter	Units	Ho, 1988	Study #04-3082						Study #824-016				Berg, 1993 and NIH Study	
Species		New Zealand rabbit	Beagle dog						Beagle dog				Rhesus monkey	
N/dose		2 (M)	6 (F)						4 (M and F)				3 (M)	
PK		CA	CA						NCA				CA	
Route		i.v.	i.v.			i.m.			i.v.				i.m.#	i.m.ç
Dose	UI/kg	40	26	87	260	26	87	260	100 (F)	100 (M)	500 (F)	500 (M)*	208	208
Dose	UI/m^2	480	520	1,740	5,200	520	1,740	5,200	2,000	2,000	10,000	10,000	2,500	2,500
Cmax	UI/mL	-	0.66	1.88	4.64	0.53	1.41	4.45	2.12	1.66	8.48	11.40	-	-
tmax	d	-	-	-	-	12.0	6.5	17.2	0.76	0.08	1.51	1.26	-	-
AUC_{last}	d*UI/mL	-	-	-	-	-	-	-	10,032	8,640	39,840	53,520	-	-
AUC_{INF}	d*UI/mL	8,155	2,496	11,064	24,624	2,832	10,608	26,544	14,376	12,648	53,760	97,200	53.0	51.0
AUC/Dose	(d*UI/mL)/(UI/kg)	204	96	127	95	109	122	102	144	126	108	194	0.3	0.2
t1/2	d	5.98	4.54	7.17	6.42	6.17	8.79	6.71	7.67	8.58	5.79	11.71	5.50	6.67
Vss or Vz/F	mL/kg	-	39.5	46.8	56.0	-	-	-	48.1	56.7	51.8	50.1	-	-
CL or CL/F	mL/d/kg	2.80	6.00	4.56	6.24	-	-	-	4.08	4.70	6.00	3.14	3.92	4.08
CL or CL/F	mL/h/kg	0.12	0.25	0.19	0.26	-	-	-	0.17	0.20	0.25	0.13	0.16	0.17
Absolute availability	%	100	100	100	100	114	96.0	108	100	100	100	100	-	-

#: Batch A9 (Supplier M); ç: Batch PD (Supplier K); CA: compartmental analysis; NCA: non-compartmental analysis; M: male; F: Female.

* one dog excluded from case sensitive parameter means (i.e. $t_{1/2}$, Vss or Vz, CL), because not reliable estimation of elimination rate constant

Distribution

The observed Vss evaluated in rats and dogs corresponded to about the plasma/blood volumes in the respective species, indicating that PEG-L-asparaginase showed a low propensity to distribute outside the systemic circulation (Studies #04-2861, #824-015, #824-015 and #824-016).

Few information are available regarding the tissue distribution of PEG-L-asparaginase in animals. Asparaginase activity was not detected in the CSF from monkeys treated with PEG-L-asparaginase intramuscularly (Berg, 1993 and NIH Study) that it did not cross the blood CSF barrier.

On the other hand, as observed by Adamson, 1970, L-asparaginase activity was found in yolk sac fluid of pregnant rabbits receiving an i.v. dose of L-asparaginase on day 8 of pregnancy. Two hours after dosing the asparaginase activities in yolk sac fluid were about 10% respect to maternal plasma and eight hours after dosing L-asparaginase activity increased to about 27% in relation to that of maternal plasma at the corresponding time, indicating that at least native L-asparaginase can cross the placental barrier.

PEG-L-asparaginase might cross the placental barrier, although PEGylation interferes with the movements of large molecules through body tissues and biological barriers (Caliceti, 2003).

The volume of distribution in rats and dogs indicates that PEG-L-Asparaginase does not largely distribute outside the systemic compartment.

No data about tissue distribution were submitted (see non-clinical discussion).

Metabolism and Excretion

No studies were submitted to specifically address the metabolism and excretion of PEG-L-asparaginase (see non-clinical discussion).

Other pharmacokinetic studies

No other pharmacokinetic studies were submitted (see non-clinical discussion).

2.3.4. Toxicology

The applicant provided an overview table on main adverse effects observed in the animal species used in experiments during the years.

Table 5: Main adverse effects across species in single and repeat dose non-clinical studies

Effect	Single dose						Repeat-dose				
	Mouse		Rat		Dog		Mouse	Rat		Dog	
	L-asp	PEG-L-asp	L-asp	PEG-L-asp	L-asp	PEG-L-asp	PEG-L-asp	L-asp	PEG-L-asp	L-asp	PEG-L-asp
Decreased motility	+	+	+		+						
Decreased food consumption	+		+	+	+				+		
Decreased weight/ Body weight gain	++	++	++	+	++		+	+	+	++	+
Soft stool						+					
Emesis					+					+	
Haematology						↓reticulocytes			Mild anaemia		
Spleen weight decrease		+					+		+		
Liver											
• Weight decrease		+							+		
• Transaminases									↑AST	↑AST↑ALT	↑ALT
• Synthesis				↓total protein ↓globulin ↑cholesterol		↓total protein			↑phosphatase alkaline ↓total protein		
• Histopathology		(1)					(2)	(3)		(4)	
Thymus atrophy										+	

Histopathology: (1): minor changes, without hepatocytes necrosis; (2): hydropic cytoplasmatic changes; (3): hepatocytes swelling and fatty infiltration; (4): hepatocytes fatty infiltration

Single dose toxicity

Single dose toxicity studies were conducted in rats, dogs and mice.

Table 6: Summary of single dose toxicity studies

Study reference / GLP compliance	Species / Number / Sex / Group	Dose (IU/kg) / Route	Observed max non-lethal dose (IU/kg)	Approx. lethal dose (IU/kg)	Major findings
Study #824-015 GLP	SD rats 8/sex/gp	0, 100, 500 IV	500	-	**≥ 100 IU/kg**: ↓ body weight gain and food consumption ↓ globulins and total proteins (M) **500 IU/kg**: 1 death (not considered drug-related) ↓ globulins and total proteins (M) ↑ cholesterol
Study #824-016 GLP	Beagle dogs 4/sex/gp	0, 100, 500 IV	500	-	**≥ 100 IU/kg**: Soft feces ↓ reticulocytes ↓ total protein **500 IU/kg**: Lacrimation (F)
Study #1 GLP	C3H/HeJ mice 5 F in the control gp 4 or 8 F in treated groups	0, 5000, 10000, 25000, 40000, 100000 i.p.	10000	25000	**≥ 5000 IU/kg**: ↓ body weight ↓ spleen weight **≥ 10000 IU/kg**: Liver changes: Hepatic nuclear polyploidy, sinusoidal leukocyte infiltration (at 10000 and 25000 IU/kg) Portal fibrosis (10000 IU/kg) Scattered periportal hepatocytes undergoing lipoid degeneration (100000 IU/kg) **≥ 25000 IU/kg**: Mortality (3 animals at 25000 and 2 at 100000 IU/kg) Decreased activity, piloerection, hunched posture

M: males F: females

PEG-L-asparaginase did not induce mortality in rats and dogs up to 500 IU/kg. In mice, deaths occurred at 250000 IU/kg and higher. PEG-L-asparaginase induced liver toxicity especially in mice and had some effects on hematology parameters (decreased reticulocytes in dogs) and lymphoid organs (decreased spleen weight in mice).

Repeat dose toxicity

Table 7: Summary of repeat-dose toxicity studies

Report No, year GLP compliance	Species/ Number/Sex/ group	Test substance Dose (IU/kg) Route	Duration	NOAEL (IU/kg)	Major findings
Study #5, 1986 GLP	Swiss Webster Mouse 5/sex/gp	PEG-L-Asparaginase 0, 50, 200, 500 i.m. 0, 50, 200, 500 i.p. Weekly	17 weeks (i.m.) 13 weeks (i.p.)	200	**i.m. administration** **≥ 50 IU/kg**: Increased activity **≥ 500 IU/kg**: ↓ body weight gain (F) **i.p. administration** **≥ 50 IU/kg**: Increased activity **≥ 500 IU/kg**: ↓ body weight gain (F) ↓ spleen weight Periportal feathery hydropic cytoplasmic changes Periportal hepatocellular atrophy Animals from the different groups died following infections (considered not treatment-related).
Study #2, 1983 GLP	Wistar Rat 6/sex/gp	PEG-L-Asparaginase 0, 10, 30, 60 5 times a week i.p.	4 weeks	60	9 animals died from pneumonia (1 control male, 1 F in the LD group, 5M + 2F in the HD group including 4 M during the 1st week) Blood in urine in all groups including control. **≥ 10 IU/kg**: ↓ spleen weight
Study #3, 1983 GLP	Wistar Rat 6/sex/gp in the control group 8/sex/gp in the treated groups	PEG-L-Asparaginase 0, 100, 200, 400 5 times a week i.m.	4 weeks	400	9 animals died from pneumonia (1M+1F in control group, 3M+1F in the LD group, 1M in the MD group and 1M + 1F in the HD). Almost all urine samples contained traces of blood, protein and ketones. **≥ 100 IU/kg**: ↓ body weight gain (F) ↑ ALP (F) ↓ spleen weight ↓ mean corpuscular volume ↓ haemoglobin (F) **≥ 200 IU/kg**: ↓ hematocrit and haemoglobin (F) **400 IU/kg**: ↑ BUN (M) ↑ AST (F) ↓ total proteins ↓ liver weight (F)

Study#8, 1984 GLP	SD Rat 6/sex/group in the control group 12/sex in the treated group	PEG-L-Asparaginase 0, 400 5 times a week i.p.	4 weeks	400	This study is a partial repetition of study #3 where a high mortality rate was observed. **400 IU/kg**: Body weight loss and suppressed food intake during the 1st week and ↓ weight gain and food intake during the rest of the study. ↓ leucocyte count (1F) ↑ bilirubin and GGT (1M) ↑ BUN (1F) ↓ spleen weight
Lorke, 1970 Not GLP	Rat (strain not specified) 10/sex/group	L-Asparaginase 200, 800, 3000 5 times a week i.p.	3 months	Not determi-nable	**≥ 800 IU/kg**: ↓ body weight gain **Dose not reported** Swelling of the liver cells with periportal fatty infiltration. Broadening of thymus cortex.
Study#4a, 1983 GLP	Beagle Dog 1/sex/gp (No histopathology examination)	PEG-L-Asparaginase 200 i.v., 200 i.p. Once a week	2 weeks	200	↓ total leucocytes after the 1st injection only. ↑ ALT (1M i. m.)
Study#4b, 1983 GLP	Beagle Dog 1/sex/gp (No histopathology examination)	PEG-L-Asparaginase 1200 i.v., 1200 i.p. Once a week	2 weeks	1200	↓ body weight gain during treatment ↑ ALT (1M i. m.) ↓ leucocytes (i.m.)
Lorke, 1970 Not GLP	Dog (breed not specified) 3/sex/gp	L-Asparaginase 200, 800, 3000 5 times a week i.v.	3 months	Not determi-nable	**≥ 200 IU/kg**: ↓ body weight gain or weight loss **3000 IU/kg**: Vomiting Fatty infiltration of the liver cells. **Dose not reported** ↑ BSP retention (1 animal) ↑ AST and ALT (1 animal) Thymus atrophy

Genotoxicity

Table 8: Summary of genotoxicity studies

Type of test / study ID / Year / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results
Ames test Study #49515, 1989 GLP	S. typhi TA97a, TA98, TA100, TA102 Plate incorporation	PEG-L-Asparaginase : 75 UI/mL +/- S9	**Negative**
Karyotypes assessment Adamson, 1970 Not GLP	Pregnant New Zealand rabbits and their fetuses Micro-blood cultures obtained from adult male and female rabbits	L-Asparaginase : 50 or 100 IU/kg IV on GD8 and GD9 Blood collected on GD28 L-Asparaginase : 0.002 to 20 IU/mL during 48 hrs	**Negative** Pregnant does and exposed fetuses had normal karyotypes. WBC had decreased mitotic activity but they had normal karyotypes

Carcinogenicity

No studies were submitted (see non-clinical discussion).

Reproduction Toxicity

No studies were submitted with PEG-L-Asparaginase. *In vitro* and *in vivo* published studies on L-Asparaginase were submitted.

Table 9: Summary of reproductive and developmental toxicity

Study type / Study reference / GLP	Species; Number / sex / group	Drug substance Dose Route	Study design	NOAEL (IU/kg)	Major findings
EMBRYO-FETAL DEVELOPMENT					
Rat embryos *in vitro* Sanfeliu, 1986 Not GLP	Albino rat embryos aged 9.5 and 10.5 days	L-Asparaginase 1.5 IU/mL in culture medium	Embryos exposed 24h or 48h	-	Embryos of 9.5 days: growth and development retardation, malformations of the brain, eyes, face and trunk, vascular dilatations at the cephalic level. Embryos of 10.5 days: minor differences in growth and protein content.
Rat embryos *in vitro* Sanfeliu, 1989 Not GLP	Albino rat embryos aged 10.5 and 11.5 days	L-Asparaginase 0.05, 0.25 or 1.5 IU/mL in culture medium	Embryos exposed 24h or 48h	-	Embryos of 10.5 days exposed 24h: malformations (partial or total absence of neural tube closure, absence of turning, facial malformations. Deformation of visceral yolk-sac. Embryos of 10.5 days exposed 48h: decreased crown-rump length, malformations (failure of neural tube closure, absence of turning, facial malformations, anophtalmia) Deformation of visceral yolk-sac.
Embryotoxicity study Adamson, 1970 Not GLP	Sprague Dawley rats (16 in the control group, 13 in the 10 IU/kg group, 7 in the 1000 IU/kg group)	L-Asparaginase 0, 100 or 1000 IU/kg IV	GD7 and GD8	1000	No teratogenic, nor embryotoxic effects
	New Zealand rabbits (8 in the control group, 4 in the 50 IU/*kg E. coli* ASNase group and, 14 in the 100 IU/kg group with *E. coli* ASNase, 3 in the 100IU/kg group with crystalline *E.coli* ASNase and 5 in the 100 IU/kg *E. carotovora* ASNase	L-Asparaginase 0, 50 or 100 IU/kg IV	GD8 and GD9	< 50	**At ≥ 50 UI/kg**: resorptions Malformations (bladder, intestines, liver, tail, limbs, brain, kidney, lung)
Teratogenic effects Lorke, 1970 Not GLP	Rats 10/gp	L-Asparaginase 0, 300, 1000, 3000, 10000 UI/kg Route not specified	GD6 to 15	Maternal 1000 Develop-mental < 300	**Dams** **At ≥ 3000 UI/kg**: ↓ weight gain **Fetuses** **At ≥ 300 UI/kg**: ↓ number of fetuses **At ≥ 1000 UI/kg**: ↓ fetal weight Malformations (microphtalmia, malformation of the vertebral column, exentria, sternal cleft) **At 10000 UI/kg**: no fetuses

Toxicokinetic data

Table 10: Exposure margin based on AUC and Cmax

Type of study	Species	Duration	NOAEL (IU/kg)	AUC (IU.h/mL) at NOAEL[a]	Asparaginase activity (IU/mL) at NOAEL[a]	Exposure margin[b] based on	
						AUC	**Cmax**
Repeated dose	**Rat**	**4 weeks**	400	-	20.51	**-**	**17**
	Dog	**2 weeks**	1200	-	21.87 (M)	**-**	**18**
				-	17.71 (F)	**-**	**15**

[a:] AUC and Cmax on the last time point. Unbound average values are given.
[b] Animal/human exposure ratios calculated from PEG-L-Asparaginase human values of C_{max} = **1.2 IU/mL** and AUC = **IU·h/mL** after administration of 2500 IU/m² i.m. (Studies ASP-302 and ASP-304).

Table 11: TK parameters from study 824-015 (rats)

Treatment	Group	Dose (IU/kg)	Gender	AUC_{last} (mIU•h/mL)	C_{max} (mIU/mL)	t_{max} (h)	$t_{1/2}$ (h)
EZN-002	2	100	Female	93500 (46100)	974 (480)	15.9 (11.3)	79.5 (16.1)
			Male	163000 (22700)	1360 (298)	10.7 (11.3)	68.1 (6.47)
	3	500	Female	720000 (199000)	5910 (2510)	15.2 (12.2)	77.6 (12.2)
			Male	726000 (188000)	6030 (1890)	12.1 (12.7)	74.9 (10.7)

Table 12: TK parameters from study 824-016 (dog)

Treatment	Group	Dose (IU/kg)	Gender	AUC_{last} (mIU•h/mL)	C_{max} (mIU/mL)	t_{max} (h)
EZN-002	2	100	Female	418000 (70700)	2120 (248)	18.3 (35.8)
			Male	360000 (65000)	1660 (352)	1.83 (2.8)
	3	500	Female	1660000 (361000)	8480 (1270)	36.3 (41.2)
			Male	2230000 (165000)	11400 (3660)	30.3 (59.8)

Based on Cmax, animals treated in the 4-week rat studies and in the 2-week dog studies were exposed at higher levels than clinical exposure.

In the 4-week rat studies, several animals died from pneumonia including animals from the control group. A non-consistent decrease in white blood cells was also observed accompanied by a decreased spleen weight without histopathology changes.

Local Tolerance

The local tolerability after intramuscular administration of PEG-L-asparaginase was investigated in a 17-week toxicity study in mouse (Study #5). Gross pathology and histopathology of the injection site indicated that the test material was well tolerated.

Other toxicity studies

Antigenicity

Study #29 was conducted according to GLP to compare the immunogenic properties of PEG-L-asparaginase with those of native L-asparaginase. Eight mice per group were injected 525 IU/kg of either PEG-L-asparaginase i.p., PEG-L-asparaginase i.m. or native asparaginase i.p. for 12 weeks.

By week 3, mice immunized with native L-asparaginase demonstrated the presence of antibodies. By contrast mice treated with PEG-L-asparaginase by either the i.p. or i.m. route had antibody titres below 1:50 throughout the study.

Immunotoxicity

No studies were submitted (see non-clinical discussion).

Dependence

No studies were submitted (see non-clinical discussion).

Metabolites

No studies were submitted (see non-clinical discussion).

Studies on impurities

No studies were submitted (see non-clinical discussion).

Other studies

PEG- toxicity

The presence of such vacuolations was verified in 3 studies in rat (Studies #2, #3 and #8) where PEG-L-asparaginase was given 5 days a week for 4 weeks, and in one study in mice (Study #5) where PEG-L-asparaginase was given once a week for 13 or 17 weeks i.p. or i.m., respectively.

During routine examination, no histopathological lesions were identified in brain or kidney.

2.3.5. Ecotoxicity / environmental risk assessment

The active substance, PEG-L-asparaginase, is a naturally occurring protein chemically modified by covalent binding with monomethoxy polyethylene glycol succinimidyl succinate (SS-mPEG).

PEGylation of therapeutic proteins is an established practice to alter pharmacokinetic properties and reduce unwanted immunogenicity and antigenicity by attachment of an inert and hydrophilic polymer to the target protein. The selected polymer, polyethylene glycol, is a hydrophilic and low-toxic compound which is used for a large variety of applications, across many industries (Davis, 2002).

The Applicant has performed a phase I calculation of the predicted environmental concentration in surface water (PECsw) for PEG, which resulted in a value that is lower than the action limit of 0.01 µg/L. Therefore a Phase II ERA is not required. This is acceptable according to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 21*).

In conclusion PEG-L-asparaginase is not expected to pose a risk to the environment following its prescribed use in patients.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The PEGylation of L- asparaginase is not expected to influence the mechanism of action of L-asparaginase. Since Oncaspar (PEGylated L- asparaginase manufactured by ENZON using native enzyme produced by Supplier M) has been approved and used in Germany, Poland and US for many years, no new PD studies were carried out which is considered acceptable.

The submitted non-clinical studies are mainly old (1980s) published studies and thus they do not comply with up to date standards. In particular, the first three studies, described in Abuchowski et al. 1984, employed batches produced at Rutgers University for which a complete physico-chemical characterization is not available. Thus, these additional (older) studies cannot support the present application. However, a large clinical experience exists since Oncaspar is marketed in the US and in Germany since 1994. Therefore no additional non-clinical studies are considered needed.

In studies with mice inoculated lymphoma or lymphosarcoma cells, PEG-L-asparaginase showed greater efficacy than native asparaginase at the same dose. PEG-L-asparaginase showed also greater efficacy when administered via the i.p. route than via the i.m. route.

In studies with dogs bearing spontaneous lymphosarcomas, PEG-L-asparaginase alone or in combination with chemotherapy induced complete or partial responses even in dogs that received prior chemotherapy. PEG-L-asparaginase was generally well tolerated but adverse effects were observed in single dogs: fatal tumour massive breakdown, disseminated intravascular coagulation, anaphylactic reactions.

No study aimed at predicting potential off-target effects of PEG-L-asparaginase was performed. However due to extensive clinical experience, the toxicological profile in patients overcomes the need for secondary PD evaluation for PEG-L-asparaginase.

The applicant did not conduct dedicated safety pharmacology and relied on repeat-dose toxicity studies and a pharmacological study. No effects on behaviour, coagulation, cardiac and respiratory systems were observed according to the submitted studies.

No non-clinical PD interaction studies were submitted with Oncaspar. The Applicant has described the potential for pharmacodynamic interactions with other chemotherapeutic agents on the basis of limited published data. This is acceptable given the significant clinical experience with Oncaspar.

Pharmacokinetics

PEG-L-asparaginase pharmacokinetics were studied in mice, rats, dogs, rabbits and monkeys through i.v., i.m. and/or i.p. routes.

Compared to native L-asparaginase, PEG-L-asparaginase showed a longer half-life (2-4 days in rodents and 5-12 days in non-rodents), a greater exposure at the same dose and it seems that immunisation had no effect on PEG-L-asparaginase clearance in mice.

PEG-L-asparaginase PK profile was comparable in mice after i.v. or i.p. administration.

The exposure was dose-proportional in rat and dogs. In the rat, there was no gender-related difference in exposure at high doses whereas male exposure was greater than female exposure at lower doses. In the dog, exposure was generally similar in males and females except in one study at high doses where male exposure was greater than female exposure at lower doses.

After PEG-L-asparaginase administration, asparaginase activity was dose-dependent in rat and can be detectable during a prolonged period in mice and rabbits. PEG-L-asparaginase induced a prolonged depletion in plasma asparagine levels that started very shortly after administration. In rat, no depletion in glutamine levels was observed.

A study in monkeys compared PEG-L-asparaginase produced using two different suppliers of native L-asparaginase, Supplier M and Supplier K. No significant differences in PK (Cl, AUC) and in PD (asparagine depletion) were noted.

The volume of distribution in rats and dogs indicates that PEG-L-asparaginase does not largely distribute outside the systemic compartment.

No data about tissue distribution are available. PEG-L-asparaginase does not seem to cross the blood–CSF barrier and no data are available regarding the placental barrier.

There are no animal studies regarding PEG-L-asparaginase metabolism and excretion. Proteins are expected to be eliminated by liver uptake, proteolysis or clearance by the immune system. However, the latter pathway is reduced by Pegylation. PEG released from the pegylated protein is expected to be in majority excreted as unchanged material in urine.

No studies on PK drug interactions of PEG-L-asparaginase were submitted which is considered acceptable considering available clinical data in the literature.

Toxicology

Most of toxicology studies provided to characterize the PEG-L-asparaginase toxicological profile for the present application, were conducted during 1980s and early 1990s, except two more recent GLP studies performed in 2007 (Studies #824-015 and #824-016) with PEG-L-asparaginase using native enzyme produced by Supplier M.

Single dose toxicity studies with PEG-L-asparaginase did not induce mortality in rats and dogs up to 500 IU/kg. In mice, deaths occurred at 250000 IU/kg and higher. PEG-L-asparaginase induced liver toxicity especially in mice and had some effects on haematology parameters (decreased reticulocytes in dogs) and lymphoid organs (decreased spleen weight in mice).

Repeat-toxicity studies conducted with PEG-L-asparaginase indicated effects on haematology parameters (decreased RBC and leukocyte counts in rats, decreased leukocyte counts in dogs), lymphoid organs (decreased spleen weight in rats with no histological changes) and liver tissue (changes in histology in mice, increased liver enzymes in rats and dogs). However, animals in the 4-week rat studies and 2-week dog studies were exposed to higher than clinical levels of the drug.

Three months' studies with L-asparaginase in rats and dogs induced effects on the liver (fatty infiltration of the liver cells) and thymus atrophy (Lorke, 1970).

In the 4-week rat studies, several animals died from pneumonia including animals from the control group. A non-consistent decrease in white blood cells was also observed accompanied by a decreased spleen weight without histopathology changes. Asparaginase is described in literature as immunosuppressive in animal studies. With regards to the provided data, it appears difficult to assess the immunosuppressive properties from a non-clinical point of view. The immunosuppressive properties have been further addressed from a clinical perspective (see section on clinical safety).

PEG-L-asparaginase did not show genotoxicity in a non-OECD compliant Ames test and in a published study assessing its effect on karyotypes.

No carcinogenicity studies were submitted. This is in agreement with ICH S6.

Embryotoxicity studies with L-asparaginase have given evidence of teratogenic potential in rats treated from day 6 to 15 of gestation with a No Observed Effect Level (NOEL) for teratogenic effects at 300 U/kg i.v. In rabbits doses of 50 or 100 U/kg i.v. on days 8 and 9 of gestation induced viable fetuses with congenital malformations: no NOEL has been determined. Multiple malformations and embryolethal effects were observed with doses in the therapeutic range. Investigations of the effect on fertility and peri- and postnatal development were not conducted (see SmPC sections 4.6 and 5.3 and RMP).

No studies in juvenile animals were conducted. However clinical data are available to establish the safety profile in the paediatric population.

Local tolerance was investigated in mice after I.M. administration showing no gross or microscopic pathological changes.

PEG-L-asparaginase was less immunogenic than native asparaginase in mice. However, the immunogenic potential should be assessed in patients and is further discussed under the section on clinical aspects.

The presence of vacuolated cells was identified with several PEGylated proteins. Repeated parenteral administration of PEGylated proteins to animals has in some cases been associated with cellular vacuolation in macrophages and/or histiocytes in various organs. No histopathological lesions were identified in brain or kidney in studies in rat and mice.

Given the expected clearance of PEG by mammalian metabolism and the very low PEC SURFACEWATER, the risk posed to the environment by PEG modification to L-asparaginase in Oncaspar is negligible. A Phase II ERA is therefore not applicable for Oncaspar.

2.3.7. Conclusion on the non-clinical aspects

Considering the available clinical data and clinical experience with pegaspargase, the non-clinical data are considered sufficient and have been adequately reflected in the product information.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 13: Overview of efficacy studies for the first-line indication

Study ID	No. of study centres / locations	Design	Study Posology	N. Pts	M/F Age	Diagnosis Incl. criteria	Primary Endpoint
CCG-1961	Several Non-EU centers as members of Children's Oncology Group / USA, Australia, Canada	Phase III, open-label, randomized, controlled study to compare the effectiveness of standard combination chemotherapy treatment with a more intensive combination chemotherapy according to early bone marrow response	Native E.coli asparaginase (6,000 IU/m^2 IM), all patients received 9 doses (three times a week) during Induction. Oncaspar (2,500 IU/m^2 IM) up to 6 or 10 doses was administered to rapid early responder (RER) patients randomly assigned to increased intensity arms during consolidation, interim maintenance, and intensifications 1 and 2. All slow early responders (SER) received 10 doses of Oncaspar after induction Erwinia asparaginase (6,000 IU/m^2 IM) was used only if patients developed clinical signs of allergy to the native E. coli or Oncaspar preparations. .	Total patients enrolled: N=2077 Total evaluable non-hypersensitive patients: N=163 non-hypersensitive RER patients randomized to increased intensity therapy: 88/163 non-hypersensitive SER patients all assigned to increased intensity therapy: 75/163	M/F n.a. 1-21 years	Children with newly diagnosed ALL	EFS OS
CCG-1962	8 Non-EU centers	Phase II, open-label,	Oncaspar 2,500 IU/m^2 IM single	Total patients enrolled:	64/54	Children with newly	PK/PD data

	member of Children's Oncology Group / USA	randomized study to compare PEG-L-asparaginase and native E.coli L-asparaginase in the standard treatment arm of CCG-1952 study for standard-risk ALL	injections during Induction and during each of 2 Delayed Inductions Native E.coli L-asparaginase (Elaspar) 6.000 IU/m^2 IM, 9 injections over 20 days during Induction and 6 injections over 12 days during each of two delayed Inductions	N=118 Total patients randomized to Oncaspar: 59/118 Total patients randomized to Elaspar: 59/118	1-9 years	diagnosed ALL	EFS
DFCI-87-001 (ASP-301)	9 Non-EU centers within the Dana-Faber Cancer Institute ALL Consortium / USA	In vitro and in vivo sub-studies as part of the DFCI-87-001 chemotherapy trial of the Dana-Faber Institute ALL Consortium	Native E.coli L-asparaginase 25.000 IU/m^2 IM, during investigational window study Oncaspar 2,500 IU/m^2 IM during investigational window study Erwinia asparaginase 25.000 IU/m^2 IM, during investigational window study	Total patients enrolled: N=344 Total patients evaluable: N=251 Total patients randomized to Oncaspar: 84/251	M/F n.a. 9 months – 15.5 years	Children with newly diagnosed ALL	EFS
DFCI-91-01	10 Non-EU centers within the Dana-Faber Cancer Institute ALL Consortium / USA, Canada, Puerto Rico	Phase III, open-label, randomized, controlled study investigating the extension of high dose asparaginase intensification from 20 to 30 weeks together with the substitution of Prednisone with Dexamethasone during post-remission therapy. Sub-randomizations: - High dose IV 6-MP vs standard dose oral 6-MP -Native E.coli L-asparaginase vs Oncaspar - Doxorubicin IV bolus vs continuous infusion - Once-daily vs twice-daily fractionated cranial radiation	Oncaspar 2,500 IU/m^2 IM every two weeks for 15 doses during Intensification Native E.coli L-asparaginase 25.000 IU/m^2 IM every week for 30 doses during Intensification	Total patients enrolled: N=377 Total patients evaluable: N=325 Total patients randomized to Oncaspar: 106/325	199/178 0 – 18 years	Children with newly diagnosed ALL	EFS

Table 14: Overview of efficacy studies for the second-line indication

Study ID	No. of study centres / locations	Design	Study Posology	N. ALL Hypersensitive Pts / N. Total Pts	M/F Age	Diagnosis Incl. criteria	Primary Endpoint
ASP-001	1 Non-EU center / USA	Phase I/II, open-label, ascending multiple dose	Oncaspar, 500-8.000 IU/m^2, IV every 2 weeks until PD or unacceptable toxicity	1/37	17/20 15-73 years	Heavily pretreated patients with refractory Hematological Malignancies	Oncaspar MTD Response rates
ASP-001C/003C	14 Non-EC centers / USA and Puerto Rico 1 EU center / Germany	Phase II/III, open-label, non comparative compassionate use study	Oncaspar 2.000 IU/m^2, IM alone or in combination with chemotherapy, every 2 weeks or according to chemotherapy protocol, until PD or unacceptable toxicity (2.500 IU/m^2 dose allowed to one Investigator)	29/41	27/14 1-66 years	Relapsed patients with a variety of Hematological Malignancies	Response rates
ASP-102	1 Non-EU center / USA	Phase I, open-label, non-comparative study	Oncaspar 2.000 IU/m^2 (later 1.000 IU/m^2) IM every 2 weeks and Methotrexate 40-80 mg/m^2 in 4 parts every 6 hours	0/11	2/9 18-74 years	Relapsed patients with NHL and Solid Malignancies	Methotrexate plus Oncaspar MTD Response rates
ASP-201A	3 Non-EU centers / USA 2 EU centers / Germany, Netherlands	Phase II/III, open-label, multicenter, international, non comparative study	Oncaspar 2.000 IU/m^2 IM every 2 weeks (three doses in induction, continued after induction if patient profited of it), Oncaspar 10.000 IU/m^2 IV one or two times over 2 hour infusion with Vincristine, Prednison and Doxorubicin (only 3 patients)	7/42	30/12 1-43 years	Relapsed patients with ALL (n=37), T-cell Lymphoma (n=2), ANLL (n=2), AML (n=1)	Response rates
ASP-203	1 Non-EU center / USA	Phase I, open-label, non comparative study	Oncaspar 2.000 IU/m^2, IM every 2 weeks	0/21	9/12 39-81 years	Relapsed patients with NHL	Response rates
ASP-302	1 Non-EU center / USA	Phase II/III, open-label, uncontrolled study conducted in 3 phases: early, re-induction and remission therapy (maintenance)	Oncaspar 2.500 IU/m^2 IM every 2 weeks during re-induction and remission therapy (a total of 29 planned administrations)	4/21	13/8 1-35 Years	Relapsed ALL	PK data + long term safety data Response rates
ASP-304	40 Non-EU centers / USA (Pediatric Oncology Group Investigators)	Phase III, open-label, randomized, comparative study of PEG-L-asparaginase vs native E.coli L-asparaginase in combination with standard agents as second induction therapy Known hypersensitive patients were assigned directly to PEG-L-asparaginase	Oncaspar: 2.500 IU/m^2 IM (two doses: day 1 and day 15) vs Elspar: 10.000 IU/m^2 IM (twelve doses, three times a week for 26 days)	40/76	47/29 1-18 Years	Children with relapsed ALL	PK data + antibody titers Response rates
ASP-400	23 EU centers /	Phase III,	Oncaspar 2.000 IU/m^2	13/44	26/18	Children with	Response

	Germany, Netherlands	open-label, multicenter, non comparative study conducted in 3 phases: Induction, Consolidation 1 and Consolidation 2	IV infusion over 2 hours as a part of a combination regimen Induction: one administration on day 12 Consolidation 1: one administration on day 5 Consolidation 2: one administration on day 5 Consolidation 1 therapy was repeated on week 9	(51 patients enrolled, data available only for 44 patients due to lack of cooperation on the part of Investigators)	2-18 years	relapsed ALL and AUL (n=42), And NHL (n=2)	rates

2.4.2. Pharmacokinetics

Oncaspar pharmacokinetic assessments were based on an enzymatic assay measuring asparaginase activity (see SmPC section 5.2). Pharmacokinetics of asparaginase was assessed using traditional PK sampling approaches in the following clinical studies in patients (ALL and other haematological malignancies): ASP-001, ASP-302, ASP-304, CCG-1962, DFCI-87-001/ASP.301.

Absorption

Oncaspar is not absorbed by the gastro-intestinal tract. It can be administered either by intramuscular or intravenous route (see SmPC section 4.2).

In adult ALL, intravenous Oncaspar resulted in peak enzymatic activity levels and asparagine depletion within 2 hours after administration. Depletion was sustained for approximately 3 weeks with a dose of 2,000 IU/m^2. In paediatric ALL patients, asparagine depletion was maintained for approximately 5 weeks with a dose of 2,500 IU/m^2 (Douer et al, 2007; Wenner et al, 2005). In adults, the plasma half-life of a single 2,000 IU/m2 dose was longer than that seen in paediatric trials with intramuscular Oncaspar (Douer et al, 2007).

Following intramuscular administration of Oncaspar (25,000 IU/m^2), levels of activity peaked at 72-96 hours after the administration and then declined with a t1/2 of 5.73 ± 3.24 days (Asselin et al., 1993).

The mean ASNase activity over time after the first 2500 IU/m^2 dose of Oncaspar was evaluated in study CCG-1962 which is further described under clinical efficacy. In this study, the determination of asparaginase activity, anti-asparaginase antibodies and amino acids, blood was collected during induction Days 0, 7, 14, 21 and 28 and cerebrospinal fluid was collected during induction Days 0, 7 and 28. At least four blood samples were collected from 57 patients in the Oncaspar group and from 45 patients in the native E coli asparaginase group. Pharmacokinetic and pharmacodynamic analyses were conducted on the samples using a one-compartment open model to fit the serum asparaginase enzymatic activity and asparagine concentrations.

The absorption and elimination of Oncaspar were described by single exponential functions. The mean half-time of absorption from the IM injection site was 1.7 days and the elimination half-life was 5.5 days (132 hours). A one-compartment population analysis yielded an apparent volume of distribution of 1.5 L/m^2. The serum half-life for native E. coli asparaginase was 1.1 days (26 hours).

A new PK and PD analysis report was issued on March 2006 as per FDA request. The new PK analysis was carried out according to NCA and evaluated just T½ and terminal rate constant (lambda z). The mean apparent elimination half-lives of Oncaspar after a single IM injection were 5.79, 5.90 and 5.55 days during Induction, and Delayed Intensification 1 and 2 phases. The mean

apparent elimination half-life for Oncaspar across all phases was 5.75 days which is comparable to values reported in the literature for Oncaspar and approximately 5 times longer than those reported for native E coli asparaginase.

Distribution

V_d was calculated in studies ASP-001, CCG-1962, and AALL07P4. Study CCG-1962 is presented above and the other two studies are described below.

- ASP-001: V_d ranged from 1.87 to 2.55 L/m^2, and was not dose-dependent
- CCG-1962: In the first data analysis, a one-compartment population analysis yielded an apparent volume of distribution of 1.5 L/m^2.
- AALL07P4: Mean Vss was 2 L at induction and 1.8 L at consolidation.

Study ASP-001

The objectives of this trial were to define toxicities, determine the maximum tolerated dose and evaluate the clinical pharmacology and efficacy of Oncaspar administered as a 1-hour infusion every 2 weeks. This study enrolled 37 heavily pre-treated patients (17 males, 20 females) with refractory haematological malignancies ranging in age from 15 to 73 years (median 49 years). The median duration of disease was 1.6 years and a median of 8 prior anticancer drugs had been received by these patients.

The study had an open-label, ascending multiple dose design. Cohorts of 3 patients were entered at each dose level, starting at 500 U/m^2, with subsequent cohorts at higher doses until dose-limiting toxicity was observed. Dose was also escalated in individual patients until a biological effect or a dose-limiting toxicity was observed. Blood samples were taken for pharmacokinetic analysis.

Patients were eligible as follows:

- Male or female ≥15 years of age.
- Life expectancy ≥6 weeks.
- Histologically proved leukaemia or other haematological malignancy refractory to conventional therapeutic regimens and with evidence of measurable disease.

Exclusion criteria were:

- History of pancreatitis or coagulopathy.
- Chemotherapy or radiation within 3 weeks prior to study start, or failure to recover from any toxic effect of previous therapy (including insufficient time since last treatment to show expected delayed toxicities).

Patients refractive to prior native asparaginase were not excluded. The investigator was permitted to make exceptions to the entry criteria at his/her discretion.

The protocol specified a starting dose was 500 IU/m^2, which was conservative based on nonclinical data with Oncaspar and clinical experience with native asparaginase. On subsequent courses the dose for individual patients could be doubled if there was no evidence of response and no dose-limiting toxicity. If a clinically significant response was observed the patient was to receive 2 to 4 doses at the effective dose level. In patients who experienced dose-limiting toxicity after being re-treated, the Oncaspar dose was reduced by 50%. Subsequent cohorts were to be started at a dose that had been demonstrated to be safe in cohort 1. However, rather than following protocol guidelines, starting doses were selected by the investigator based on clinical judgment.

Blood samples were collected from 31 patients. There were too few samples to allow calculation of pharmacokinetic parameters in 4 patients. In addition, 2 patients who experienced anaphylactic reactions were excluded from the pharmacokinetic analysis due to rapid disappearance of the

enzyme from the circulation as a result of the immune response. Pharmacokinetic data for the remaining 25 patients are summarised below:

Table 15: Pharmacokinetics of L-asparaginase following Oncaspar administration (Study ASP-001)

Oncaspar dose (IU/m^2)		$t_{½}$ (h)	Vd (mL/m^2)	AUC (IU/m^2)day	CL $mL/m^2/day$
500	Mean	315	2,111 561	5.2	99
	SD	55		1.1	20
	CV%	17.5	26.6	21.2	20.2
1000	Mean	317	1,941 762	9.4	144
	SD	246		4.4	101
	CV%	77.6	39.3	46.8	70.1
2000	Mean	588	2,553	27.1	77
	SD	406	1,391	6.1	19
	CV%	69.0	54.5	22.5	24.7
4000	Mean	184	1,865 326	25.4	186 55
	SD	18		5.4	
	CV%	9.8	17.5	21.3	29.6
8000	Mean	415	2,143 413	89.9 43.8	117 75
	SD	255			
	CV%	61.4	19.3	48.7	64.1

Plasma versus time profile for Oncaspar was monophasic with a mean elimination half-life across doses of 357 (±243) hours corresponding to 14.9 (±10.1) days. Peak plasma concentrations at the end of infusion trough concentrations at Day 14 and AUCs were approximately proportional to the dose. The volume of distribution and clearance were independent of the administered dose. One-way analysis of variance was performed to determine whether there was a significant difference in the half-lives across the five dose groups. Resultant F-tests showed that there were no differences (F=1.604; p=0.213). At the higher dose levels, 2-weekly dosing could potentially result in significant accumulation of asparaginase.

Study AALL07P4

This was a multicentre, randomised, open-label, active comparator controlled trial in patients (>1 year and <31 years of age at the time of diagnosis) with newly diagnosed high-risk B-precursor ALL. Eligible patients were randomised in a 2:1 ratio to receive the experimental drug at a dose of 2100 IU/m^2 or 2500 IU/m^2 IV or Oncaspar 2500 IU/m^2 IV plus full augmented BFM Berlin-Frankfurt-Münster (BFM) multi-agent chemotherapy. It was planned to recruit 186 patients (62 randomised to Oncaspar).

The study design includes a 35-day Induction period, a 2-week Extended Induction period (for patients with M2 marrow or marrow with ≥1% MRD), an 8-week Consolidation period, up to two 8-week IM periods, up to two 8-week drug induction (DI) periods, and Maintenance therapy. Maintenance therapy consists of repeated 12-week cycles. The total duration of therapy is 2 years from the start of Interim Maintenance I for female patients and 3 years from the start of Interim Maintenance I for male patients.

Rapid early responders (RER) received one IM and one DI phase, and those classified as slow early responders (SER) and/or CNS3 positive received two IM, two DI phases. PEGylated asparaginase was administered on Day 4 of Induction, on Day 4 of Extended Induction (if applicable), on Days

15 and 43 of Consolidation, on Days 2 and 22 of both Interim Maintenance periods, and on Days 4 and 43 of both DI periods. All patients had PK and PD evaluations after administration of randomised study drug on Days 4, 5, 6, 8, 15, 22, and 29 of Induction, and Days 15, 16, 17, 22, 29, 36, and 43 of Consolidation. Evaluation of minimal residual disease (MRD) was performed at induction Day 29.

All patients were to have had a complete PK and PD evaluation after administration of calaspargase pegol or Oncaspar on induction Day 4 and Consolidation Day 15 until it had been determined that 135 patients were evaluable for full PK analyses.

Table 16: Pharmacokinetics of L-Asparaginase following Oncaspar administration in induction phase (Study AALL07P4)

PK Parameter		Oncaspar 2500 IU/m^2 (N = 43)
C_{max} (mIU/mL)	n	43
	Mean ±SD	1646.7 ± 473.87
t_{max} (h)	n	43
	Mean ±SD	3.8 ± 6.22
AUC_{0-t} (mIU*h/mL)	n	43
	Mean ±SD	359780.9 ± 80308.63
AUC_{0-25d} (mIU*h/mL)	n	43
	Mean ±SD	365021.2 ± 76981.41
$AUC_{0-\infty}$ (mIU*h/mL)	n	43
	Mean ±SD	387014.9 ± 85752.87
Kel (1/h)	n	43
	Mean ±SD	0.0061 ± 0.00173
$t_{1/2}$ (h)	n	43
	Mean ±SD	126.9 ± 50.51
CL (L/h)	n	43
	Mean ±SD	0.0091 ± 0.00501
Vss (L)	n	43
	Mean ±SD	2.0 ±1.20

Table 17: Pharmacokinetics of L-Asparaginase following Oncaspar administration in consolidation phase (Study AALL07P4)

PK Parameter		Oncaspar 2500 IU/m^2 (N = 43)
C_{max} (mIU/mL)	n	29
	Mean ±SD	1477.5 ± 291.62
t_{max} (h)	n	29
	Mean ±SD	7.7 ± 11.84
AUC_{0-t} (mIU*h/mL)	n	30
	Mean ±SD	407922.9 ± 146368.83
$AUC_{0-\infty}$ (mIU*h/mL)	n	24
	Mean ±SD	441216.4 ± 109395.84
Kel (1/h)	n	24
	Mean ±SD	0.0066 ± 0.00195
$t_{1/2}$ (h)	n	24
	Mean ±SD	117.2 ± 49.36
CL (L/h)	n	24
	Mean ±SD	0.0078 ± 0.00517
Vss (L)	n	24
	Mean ±SD	1.8 ±1.38

Means in those two tables are arithmetic means.

Exploratory analysis of PK parameters were performed based upon age, sex, and race. There was a limited number of patients in each group after the stratification. The following age–related trends were noted across all 3 treatment groups:

- The mean C_{max} appeared to be higher in the youngest age stratification (1 to <3 years) and tended to decrease with age in the older age stratifications.
- The mean V_{ss} appeared to be the least in the youngest age stratification and tended to increase with age in the older age stratifications.
- The mean AUC values showed a tendency to be higher in the lower age stratifications. This trend was more apparent with AUC_{0-25d} as compared to $AUC_{0-\infty}$ and AUC_{0-t}.
- The mean CL appeared to be the least in the youngest age stratification and tended to increase with age in the older age stratifications.

In the Oncaspar group, there appeared to be an age-related increase in half life. The youngest age stratification (1 to <3 years) had the shortest mean half-life (106 hours) with the half-life increasing with increasing age to a mean half-life of 156 hours in the oldest age stratification (≥16 years).

The overall PK-evaluable population was evenly balanced between male (n=74) and female (n=71) patients. There were no clear trends that would suggest gender differences in the PK of asparaginase activity with the exception of CL and Vss, which were slightly higher in males than in females.

Most patients in the PK-evaluable population in the calaspargase pegol and Oncaspar were white (122/145, 84%). The limited number of patients in other race groups (10 Black or African American, 2 native Hawaiian or other Pacific Islander, with 7 unknown and 2 other, not specified) was too limited to support discussion of race differences on PK of asparaginase activity.

Elimination

Excretion pathways

During Study ASP-001, asparaginase was not detected in urine samples collected from the first 9 patients to be studied.

During Study ASP-301, an ELISA was used to determine whether asparaginase protein could be detected in the urine samples of two patients. Results showed that only extremely low levels of asparaginase are detectable in urine (0.15 IU in a 24-hour sample, equivalent to 0.1% of the administered dose).

No human mass-balance studies were provided.

The disappearance of L- asparaginase activity from blood is at least partly due to the distribution of the enzyme into the extravascular fluid and clearance via the reticuloendothelial system. In one study in humans, the results of serum and urine ELISA suggest that PEG-L-asparaginase activity and the protein were cleared by mechanisms other than urinary excretion (Asselin, 1993). Possible mechanisms that are consistent with the results of this study include proteolysis of the enzyme and/or removal by an organ other than the kidneys. Authors suggested that, although previous reports suggest this might not be the case, PEG-L-asparaginase may be metabolized by the liver, excreted in the bile, or filtered from the plasma by the RES (Asselin, 1993).

There are no data presented on the metabolism of the PEG associated with PEGylated proteins; information reported in literature suggests that urinary excretion of unchanged material will be the major route of clearance of any PEG released by degradation of conjugate. Human excretion balance studies have shown that 86% and 96% of PEG 1000 and PEG 6000 were excreted into the urine 12 hours after an intravenous administration. Biliary excretion of unchanged material would be expected to be a minor route (Webster, 2007).

Terminal half-lives

Terminal half-lives were calculated in all the studies below.:

- ASP-001: $T_{1/2}$ was estimated to be 357 (±243) hours, corresponding to 14.9 (±10.1) days, and was independent of dose.
- ASP-301: $T_{1/2}$ was estimated to be 5.73 ± 3.24 days with all patients, or 1.82 ± 0.26 days, in hypersensitive patients.
- ASP-302: $T_{1/2}$ was estimated to be 2.69 ± 1.97 days (ranging from 1.17 to 5.90 days) in hypersensitive patients, and 4.83 ± 2.62 days (ranging from 0.79 to 17.93 days) in non-hypersensitive patients.
- ASP-304: $T_{1/2}$ was estimated to be 2.88 ± 2.40 days in hypersensitive patients (ranging from 0.41 to 7 days), and 3.41 ± 1. 75 days (ranging from 0.91 to 6.44 days) in non-hypersensitive patients. Clearance was also faster, and $T_{1/2}$ shorter, in patients with high antibody levels, especially those who are hypersensitive.
- CCG-1962: $T_{1/2}$ was estimated to be 5.79 days, 5.90 days and 5.55 days during Induction, and Delayed Intensification 1 and 2 phases. However, there was an outlier at induction with a terminal half-life of 215.7 days.
- DFCI-87-001: $T_{1/2}$ was estimated to be 5.73 ± 3.24 days. Finally, in patients with low antibody titres the mean half-life of Oncaspar was 7.05 days. This compared with a mean of 2.59 days in high titre patients.
- AALL07P4: $T_{1/2}$ was estimated to be 126.9 ± 50.51 hours (5.29 ± 2.10 Days) in induction phase and 117.2 ± 49.36 hours (4.88 ± 2.06 Days) in consolidation phase.

Comparison with other L-asparaginases:

- ASP-301: $T_{1/2}$ of native enzyme preparations Elspar was 1.24 ± 0.17 days (mean ± SD) in the high-dose group and 1.35 ± 0.30 days for the low-dose group.
- CCG-1962: The serum half-life for native *E. coli* asparaginase was 1.1 days (26 hours).
- DFCI-87-001: The half-lives for the 3 asparaginase preparations were statistically significantly different, with Oncaspar (5.73 ± 3.24 days) having a much longer half-life than the native enzyme preparations Elspar (1.28 ± 0.35 days) and Erwiniase (0.65 ± 0.13 days).

Study ASP-301

The objectives of this study were to determine the half-life of 3 different asparaginase preparations (asparaginase activity and protein level) and to examine the effect of single dose, repeated doses and hypersensitivity on the half-life of serum asparaginase activity in paediatric population. The three asparaginases investigated were:

- Oncaspar
- Native E coli L-asparaginase (Elspar).
- Native Erwinia L-asparaginase.

After obtaining informed consent, children with newly diagnosed ALL were treated intramuscularly according to one of two sequential treatment protocols:

- Between 1985 and 1987, patients were randomized to receive 25,000 IU/m^2 (high dose) or 2,500 IU/ m^2 (low dose) native E coli asparaginase as a single IM injection on the first day of therapy (Day 0).
- Between 1987 and 1991, the randomization was between the following treatments:
  - 25,000 IU/ m^2 native E coli asparaginase
  - 25,000 IU/ m^2 native Erwinia asparaginase
  - 2,500 IU/ m^2 Oncaspar

On Day 5, patients received five-agent induction therapy (vincristine, prednisone, doxorubicin, methotrexate and intrathecal cytarabine). Blood samples for analysis were drawn on Days 0 to 6, and then every 2 to 3 days through Day 26.

Induction therapy was followed by multiple-drug intensification therapy, featuring administration of intensive native E coli asparaginase 25,000 IU/m^2 IM weekly for at least 20 weeks but not longer than 36 weeks. Intensification therapy included cranial irradiation and combination chemotherapy with standard agents. For middle-dose studies, blood was obtained on each of 4 or 5 days in the 1-week interval following one of the doses of asparaginase between the third and fifteenth dose. Blood samples for last-dose studies were obtained in the same manner following the final dose of asparaginase (usually the 20th to 36th dose of weekly asparaginase).

Twenty-four-hour urine samples were collected from two patients for 6 days following a single dose of 25,000 IU/ m^2 native E coli asparaginase, concentrated approximately 15 times, and tested by ELISA.

Effect of dose on serum asparaginase activity:

In the first part of the study, 17 patients received high-dose native E coli asparaginase (25,000 IU/m^2) and 16 patients were treated with the lower dose of 2,500 IU/m^2. The decrease in serum asparaginase activity after the initial dose is shown in the figure below. The regression equation was calculated for Days 2-12 and Days 2-8 for high-dose and low-dose, respectively.

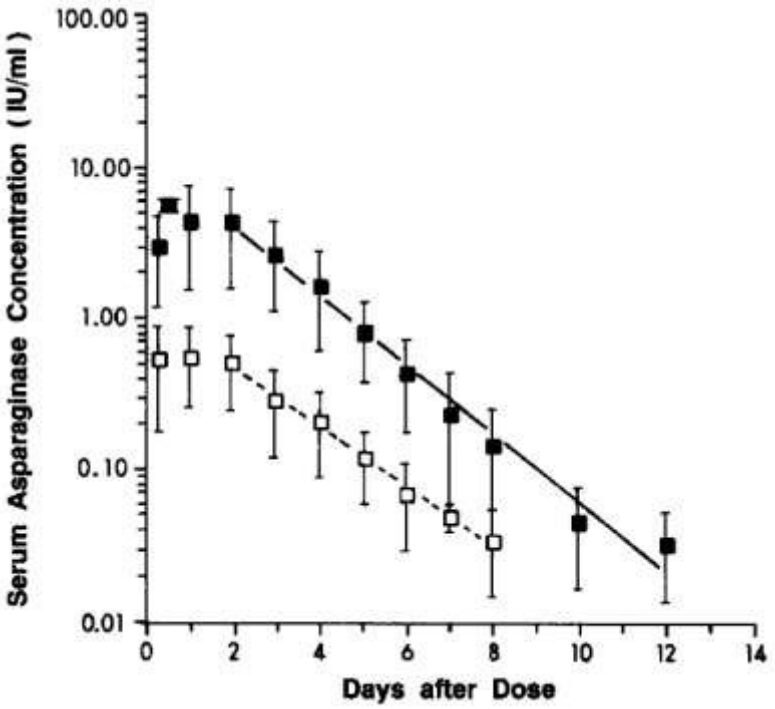

Figure 1: Serum asparaginase (IU/mL) vs time curve following IM E. coli asparaginase treatment (□ 2,500 UI/m^2; ■ 25,000 UI/m^2) (ASP-301)

The correlation coefficient was highly significant for both regression lines (r=0.99). The doses administered differed by one order of magnitude and the extrapolated maximum serum levels (y-intercept) also differed by approximately an order of magnitude. For both groups, the peak serum level was achieved at 24 to 48 hours. Asparaginase activity was no longer detectable in sera by Day 10 (low-dose group) or Day 14 (high-dose group). The limit of detection for the assay was 0.01 IU/mL.

The serum half-lives were 1.24 ± 0.17 days (mean ± SD) in the high-dose group and 1.35 ± 0.30 days for the low-dose group. The between-group difference in half-life was not statistically significant (p=0.2).

The calculated half-lives for patients in each group were examined for the effect of age, sex and risk-category classification according to Clavell et al, 1986. No difference in apparent T½ was seen for patients aged <2 years as compared with those aged ≥2 years (p>0.2). Similarly, there was no difference in T½ according to gender (p>0.5) or standard risk vs high risk or vs very high risk (p>0.15).

Apparent T½ of asparaginase protein:

Sera from eight patients were examined by both the activity assay and ELISA for protein determination. Five of these patients received high-dose asparaginase while the other three were randomised to the low dose. Similar to the enzyme activity, asparaginase protein was no longer detectable in sera by Day 9 in the low-dose group or by Day 14 in the high dose group. A log-linear rate of decrease in serum levels was observed for both the asparaginase activity and the protein itself. Mean half-lives calculated for each group are shown in the table below.

Table 18: Serum T½ of asparaginase activity vs asparaginase protein following IM E. coli asparaginase treatment (ASP-301)

Population	$T_{½}$ (days)		
	Activity (mean ± SD)	Protein (mean ± SD)	P-value*
All patients (n=8)	1.44(± 0.35)	1.27(± 0.12)	p=0.21
High-dose (25,000 IU/m^2; n=5)	1.34(± 0.34)	1.28(± 0.13)	p=0.65
Low-dose (2,500 IU/m^2; n=3)	1.62(± 0.34)	1.24(± 0.14)	p=0.30

* Determined by paired Student's t test; statistically significant where p≤0.05

There was no statistically significant difference between the T½ of the immunologically detectable asparaginase molecule compared with the enzymatic activity.

An ELISA was used to determine whether asparaginase protein could be detected in the urine samples of two patients. Results showed that only extremely low levels of asparaginase are detectable in urine (0.15 IU in a 24-hour sample, equivalent to 0.1% of the administered dose).

Effect of repeated doses on serum asparaginase activity:

The serum asparaginase activity were determined in blood samples collected over the time in patients receiving single and multiple doses of E. coli asparaginase. The mean T½ of the first dose of native E coli asparaginase for 9 patients was 1.21 days (SD ± 0.17 days).

The T½ in these same 9 patients was re-assessed during intensification after 1-14 previous doses. The mean T½ after repeated doses was 1.28 days (± 0.35 days). There was no statistically significant difference between these half-lives (p=0.7).

Serum asparaginase was then measured following the final (20th - 30th) intensification asparaginase dose. The mean T½ after the final dose was 1.14 days (± 0.28 days). Again, there were no statistically significant differences between the half-life after the first dose (p=0.3) or after middle doses (p=0.4).

Effect of asparaginase preparation of serum asparaginase activity:

In the second part of the study, the pharmacokinetics of the 3 different asparaginases were compared (n=10 for each asparaginase preparation).

For native Erwinia asparaginase, serum activity levels were highest at initial sampling within 24 hours after the dose and were no longer detectable by Day 7. The mean and standard deviation of T½ was 0.65 ± 0.13 days. This is significantly shorter than the T½ for native E coli asparaginase (p<0.001).

For Oncaspar, asparaginase activity was measurable in the serum for the entire 26-day observation period. Peak levels of activity were measured at 72-96 hours after the dose, which is slightly later than seen with native E coli asparaginase. The mean and standard deviation for T½ of enzyme activity for Days 4-26 was 5.73 ± 3.24 days, significantly greater than the T½ for native E coli asparaginase (p<0.001).

The decrease in serum activity was log-linear for all 3 enzymes during the initial 14-day observation period (see the figure below):

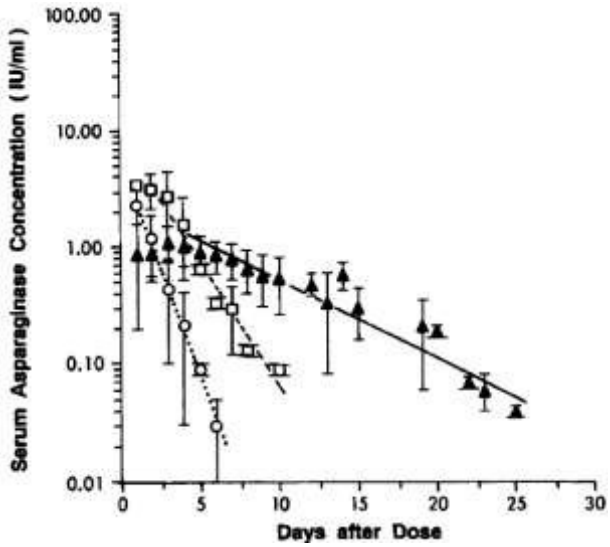

Figure 2: Serum asparaginase activity versus time profiles for patients receiving (□) IM E. coli 25,000 IU/ m2; (○) IM Erwinia 25,000 IU/ m2 or (▲) or IM Oncaspar° 25,000 IU/ m2 (ASP-301)

For 7 patients treated with Oncaspar, there were enough time points studied to allow calculation of the serum T½ between Days 4-14 and Days 15-26 separately. The mean ± SD T½ was 6.86 ± 3.08 days and 2.99 ± 1.57 days for Days 4-14 and Days 15-26, respectively. Thus, the early T½ was significantly longer than the later T½ ($p=0.001$).

Serum asparaginase activity following hypersensitivity reaction:

Ten patients with known hypersensitivity to E. coli asparaginase were studied. Five patients had one or more asparaginase level(s) obtained in the week following an apparent hypersensitivity reaction: 1 with urticaria, 1 with a few hives and 3 with a minor local reaction of redness, swelling and pain at the injection site. Two of these patients were tested 1 day after the dose and in these patients the serum asparaginase activity levels were unusually low at 0.58 IU/mL and 0.05 IU/mL. The second of these patients was also tested on Day 3 when serum asparaginase activity was found not to be detectable (<0.01 IU/mL). In 2 further patients tested on Day 3 and on Days 6 and 7, respectively, serum asparaginase activity was not detectable. Only in 1 patient tested on Day 7 the asparaginase level was within the usual range (0.09 IU/mL). Therefore, in this group of 5 patients asparaginase activity was markedly decreased when compared with predicted values in six of seven samples drawn between 1 and 7 days following the suspected reaction.

Five patients with a history of hypersensitivity reaction to the native E. coli preparation were studied following a dose of Oncaspar. As shown in the table below, enzyme activity decreased, with an apparent T½ of 1.82 ± 0.26 days. This terminal half-life is significantly shorter than that observed in patients treated with Oncaspar who had not previously received any form of asparaginase ($p<0.01$).

Table 19: Serum asparaginase $T_{½}$ in patients with known hypersensitivity to native E coli asparaginase receiving an E. coli asparaginase or Oncaspar dose (ASP-301)

Asparaginase preparation	Dose (IU/m^2)	T½ (days)	n	p-value
Native *E. coli*	25,000	undetectable	5	p<0.01
Oncaspar	2,500	1.82 (± 0.26)	5	p<0.01

Study ASP-302

The purpose of this study was to obtain pharmacokinetic and long-term safety data on Oncaspar. It was conducted in 21 relapsed ALL patients (13 male, 8 female) ranging in age from 1 to 35 years old. Four of the male patients were known to be hypersensitive to native asparaginase prior to study participation.

The study had an open-label design and was conducted in 3 phases:

- Phase I: Early therapy.
- Phase II: Re-induction therapy.
- Phase III: Remission therapy / maintenance.

Patients were eligible for inclusion if they had evidence of bone marrow relapse during or after treatment with multi-agent rotational chemotherapy. Patients were excluded if they had a history of life-threatening sensitivity to VM-26 (teniposide). A known hypersensitivity to other (non-PEGylated) forms of L-asparaginase did not exclude a patient from participation.

Oncaspar was administered IM at 2,500 IU/ m^2 every 2 weeks during re-induction and remission therapy (a total of 29 doses) as part of a multi-drug chemotherapeutic regimen.

Blood samples were collected for 11 of the 21 total patients, 2 of whom were hypersensitive. Evaluations were performed after either a single dose (n=6) or 2 doses (n=5) according to a non-compartmental approach. T½ and AUC from time 0 to infinity were calculated.

The means and standard deviations of the data set are summarised in the table below according to hypersensitivity status.

Table 20: Summary of pharmacokinetic data by hypersensitivity status (Study ASP-302)

Parameter	Hypersensitive patients (n=2)	Non-hypersensitive patients (n=9)	Total Patients (n=11)
$T_{½}$ (days) (mean ± SD)	2.69 (±1.97)	4.83 (±2.62)	4.44 (±2.58)
AUC (IU*d/mL) (mean ± SD)	3.52 (±4.23)	10.35 (±5.63)	9.11 (±5.90)

Study ASP-304

The objectives of the study were to compare the efficacy and toxicity of Oncaspar administration with that of native E coli-derived L-asparaginase when used as part of a standard combination

chemotherapy re-induction regimen in children with ALL who are in second hematologic relapse. The pharmacokinetic objectives were to determine the drug half-life for each product. In addition, antibodies to L-asparaginase were monitored in all patients.

- Patients were eligible for inclusion in the study if they met the following criteria:
- Diagnosis of ALL before age 21 years and in the second haematological relapse.
- Life expectancy ≥4 weeks.
- Adequate hepatic and renal function (SGPT <200 IU/L; creatinine <2 mg/dL).

Exclusion criteria were as follows:

- Presence of CNS disease (unless the investigator judged it appropriate to withhold intrathecal chemotherapy during the 4 weeks of Oncaspar° combination chemotherapy; intrathecal medication could be given with the screening lumbar puncture at the discretion of the physician).
- Failure of other induction regimens which contained L-asparaginase.

Patients without a history of hypersensitivity to native asparaginase (E coli or Erwinia) were randomised to receive either Oncaspar or native E coli-derived L-asparaginase (Elspar). Patients with known hypersensitivity to native enzyme were directly assigned to treatment with Oncaspar. The asparaginase treatment schedules were as follows:

- Oncaspar: 2,500 IU/ m^2 by intramuscular route on Day 1 and Day 15 (2 doses in total).
- Elspar: 10,000 IU/ m^2 by intramuscular route 3 times per week for 26 days (12 doses in total).

In common with the other pre-authorisation clinical trials, the Oncaspar used in Study ASP-304 was predominantly manufactured using asparaginase sourced from Supplier M. However, in this trial 7 patients were treated with Oncaspar manufactured using the Supplier K asparaginase (the source for commercial Oncaspar under the German and Polish MAs).

The protocol allowed patients assigned to Oncaspar to continue into maintenance therapy with Oncaspar at the discretion of the physician. Patients assigned to Elspar were also allowed to continue maintenance therapy with Oncaspar following a protocol amendment.

Plasma concentrations of L-asparaginase and anti-asparaginase antibody titres, were ascertained prior to administration of Oncaspar and on Days 1, 2, 3, 4, 8, 15, 22, 29, and 36. It was originally planned to measure plasma asparagine concentrations at the same time points but this was not done because the necessary sample preparation procedures could not be performed by the study personnel.

A total of 76 patients participated in the study (47 male, 29 female). Of these, 16 completed the trial. The remaining patients were taken out from the study for the following reasons:

- Progressive disease (n=27).
- Relapse (n=18).
- Bone marrow transplant (n=7).
- Death (n=4).
- Toxicities (n=3).
- Refusal of further therapy (n=1).

Exposure to study drug is summarised below:

Table 21: Exposure to study drug (ASP-304)

Treatment assignment	n	Total collective doses	Mean number of doses per patient	Range (min - max)
Oncaspar (directly assigned)	40	79	2.0	1 - 2
Oncaspar (randomised)	19	36	1.9	1 - 2
Elspar (randomised)	17	176	10.4	4 - 12

Pharmacokinetic parameters were calculated according to a non-compartmental approach; the AUC reported was calculated for the first dose from time 0 to last assay value prior to the second dose (AUClast).

The pharmacokinetic results for Oncaspar are summarised according to prior hypersensitivity status below:

Table 22: Oncaspar pharmacokinetic results (Study ASP-304)

Pharmacokinetic parameter	Hypersensitive patients		Non-hypersensitive patients	
	n	Mean (± SD)	n	Mean (± SD)
C_{max} (IU/mL)	30	1.07 (± 0.65)	15	1.15 (± 0.53)
AUC_{last} (IU*d/mL)	30	5.52 (± 4.20)	15	9.27 (± 5.41)
T_{max} (d)	30	2.80 (± 1.30)	15	3.27 (± 2.05)
$T_{½}$ (d)	12	2.89 (± 2.40)	8	3.41 (± 1.66)

Means are arithmetic means

Mean values for all parameters were lower for hypersensitive patients than for the non-hypersensitive group. The AUC for the hypersensitive population was close to half that for non-hypersensitive patients (5.52 IU*d/mL vs 9.27 IU*d/mL).

Experimental parameters such as AUC_{last}, T_{max} and C_{max} were calculated for all the available patients, T½ data were extrapolated could not be calculated for 18 of the hypersensitive patients and for 7 of the non-hypersensitive group. The reasons for this were:

- Too few samples available (n=14).
- No terminal elimination phase due to curve plateau (n=6).
- No terminal elimination phase due to curve dropping rapidly (n=5).

The pharmacokinetic data for the subset of the population in which a T½ could be calculated are shown below:

Table 23: Pharmacokinetic results for patients with evaluable $T_{½}$ (Study ASP-304)

Pharmacokinetic parameter	Hypersensitive patients (mean ± SD) (n=12)	Non-hypersensitive patients (mean ± SD) n=8
C_{max} (IU/mL)	1.25 (± 0.67)	0.95 (± 0.59)
AUC_{last} (IU*d/mL)	6.75 (± 4.50)	5.99 (± 4.85)
T_{max} (d)	2.67 (± 1.23)	1.88 (± 0.99)
$T_{½}$ (d)	2.88 (± 2.40)	3.41 (± 1.75)

Note: Means are arithmetic means

Antibody data were analysed to determine whether Day 14 antibody level affected the pharmacokinetics of the first Oncaspar dose.

Table 24: Pharmacokinetic data by Day 14 antibody level (ASP-304)

Patient population	Parameter	Low antibody level		High antibody level	
		n	Mean (± SD)	n	Mean (± SD)
Hypersensitive	C_{max} (IU/mL)	8	1.27 (±0.54)	22	1.00 (±0.68)
	AUC (IU*d/mL)	8	9.71 (±4.42)	22	4.00 (±2.95)
	T_{max} (days)	8	3.13 (±1.36)	22	2.68 (±1.29)
	$T_{½}$ (days)	5	3.20 (±2.15)	7	2.66 (±2.71)
Non-hypersensitive	C_{max} (IU/mL)	7	1.50 (±0.41) 13.63 (±3.14)	8	0.85 (±0.45) 5.45 (±3.79)
	AUC (IU*d/mL)	7		8	
	T_{max} (days)	7	4.71 (±1.98)	8	2.00 (±1.07)
	$T_{½}$ (days)	1	6.44 (±0.00)	7	2.98 (±1.21)
All patients	C_{max} (IU/mL)	15	1.38 (±0.48)	30	0.96 (±0.62)
	AUC (IU*d/mL)	15	11.54 (±4.25)	30	4.38 (±3.19)
	T_{max} (days)	15	3.87 (±1.81)	30	2.50 (±1.25)
	$T_{½}$ (days)	6	3.74 (±2.33)	14	2.82 (±2.02)

Study DFCI-87-001

This study investigated the pharmacokinetics, pharmacodynamics and immunogenicity of native E. coli L-asparaginase (Elspar), native Erwinia L-asparaginase (Erwiniase) and Oncaspar. The population studied was children with ALL on treatment protocols that included intramuscular asparaginase during remission induction and/or for at least 20 weeks after achieving remission. Children were treated according to one of a series of Dana Faber Cancer Institute (DFCI) or

Paediatric Oncology Group (POG) treatment protocols between 1987 and 1995. Between 1987 and 1991, patients treated under DFCI protocol 87-001 were randomised to receive one of the 3 study drugs as a single intramuscular injection on the first day of therapy as part of a 5-day investigative window. Doses administered were as follows:

- Elspar: 25,000 IU/m^2.
- Erwiniase: 25,000 IU/m^2.
- Oncaspar: 2,500 IU/m^2.

Serial serum samples were taken throughout the 26-day induction period.

Induction therapy was followed by multiple drug intensification therapy featuring intramuscular administration of Elspar (25,000 IU/m^2) weekly for at least 20 weeks. For middle and last doses, blood was obtained on each of 4 or 5 days in the 1-week dosing interval. A "middle dose" was defined as between the 3rd and 15th dose. The final dose was usually the 20th to 30th administration.

Asparaginase activity levels, asparagine concentrations and anti-asparaginase antibodies were analysed in study samples. The half-life data for the 3 study drugs are presented in the table below.

Table 25: Half-life data for asparaginase preparations; single dose (DFCI-87-001)

	Elspar (n=17)	**Erwiniase (n=10)**	**Oncaspar° (n=10)**
$t_{½}$ (days ± SD)	1.28 (±0.35)	0.65[a] (±0.13)	5.73[b] (±3.24)

[a] Half-life significantly shorter than for Elspar by student t-test ($p<0.001$).

[b] Half-life significantly longer than for Elspar by student t-test ($p<0.0001$).

The data on Elspar serum asparaginase half-life as a function of repeated dosing (n=9) were also provided. The mean half-lives for first, middle and final doses were 1.28, 1.21, and 1.14 days, respectively. The differences were not statistically significant ($p>0.3$).

In patients with low antibody titres the mean half-life of Oncaspar was 7.05 days. This compared with a mean of 2.59 days in high titre patients ($p=0.0003$).

Dose proportionality and time dependencies

Information about dose proportionality was provided from Study ASP-001. The volume of distribution and clearance were independent of the administered dose. Doses ranged from 500 IU/m^2 to 8,000 IU/m^2 given intravenously every two weeks. In 25 of 37 patients, the median half-life was 11.1 days and dose proportionality was observed.

One-way analysis of variance was performed to determine whether there was a significant difference in the half-lives across the five dose groups. Resultant F-tests showed that there were no differences ($F=1.604$; $p=0.213$).

In study ASP-301, for 7 patients treated with Oncaspar, there were enough time points studied to allow calculation of the serum T½ between Days 4-14 and Days 15-26 separately. The mean ± SD T½ was 6.86 ± 3.08 days and 2.99 ± 1.57 days for Days 4-14 and Days 15-26, respectively. Thus, the early T½ was significantly longer than the later T½ ($p=0.001$).

Model and Simulation

For study AALL07P4, a population pharmacokinetic (Pop PK) model was developed to describe the pharmacokinetics of Oncaspar, the factors affecting the variability of pharmacokinetic parameters

in this population, and to simulate single and steady state peak concentrations (Cmax) and exposure (AUC). A 2-compartment model with nonlinear clearance was found to be the best model for Oncaspar.

Table 26: Oncaspar final pharmacokinetic model parameter values

Parameter (Units)		**Population Mean (SE%)**	**%CV Inter-Individual Variance (shrinkage)**
Vmax (IU/hour)	θ_1	9.69 (4.5%)	8.8 (10.7%)
BSA Effect on Vmax	θ_7	1.04 (5.0%)	-
Km (IU/L)	θ_2	351 (10.0%)	
Central Volume (V1) (L)	θ_3	2.52 (3.5%)	16.2 (12.7%)
BSA Effect on Central Volume	θ_8	1.31 (7.4%)	-
Clearance (Q) (L/hr) Inter-compartmental	θ_4	0.024 FIX	-
Peripheral Volume (V2) (L)	θ_5	0.119 FIX	-
Residual Variability	θ_6	28.6 (1.7%)	-

Objective function = -721.635; Subjects = 44; Observations = 566 (note number of observations decreased due to removal of records with conditional weighted residuals greater than 5.
Source: Table 4, Population Pharmacokinetics Oncaspar and Calaspargase pegol Study AALL07P4.

Simulations were performed using the subjects in the model building dataset. The new virtual subjects were created by using each subject's unique covariate values at each treatment visit.

The asparaginase activity versus time profiles were generated following administration of Oncaspar on day 4 (day 0 on the plots) of induction therapy and days 15 (46 day interval) and 43 (28 day interval) of consolidation therapy. The results showed that the asparaginase activity for Oncaspar drops off rapidly.

The asparaginase activities versus time profiles were generated following multiple Oncaspar doses in order to estimate the asparaginase activity at steady state. The asparaginase activity was simulated for 1.7 years after 15 monthly (every 28 days) doses for the same dose levels as above. This long time period for the simulation was needed to estimate the $AUC_{(0\text{-inf})}$ at steady state for a different PEG-asparaginase drug that would be compared to Oncaspar in this study. Results showed that with this dosing interval and duration, a little accumulation was apparent for Oncaspar.

The AUC and C_{max} values at steady state were also determined from the simulated data. The results are summarised in the table below.

Table 27: Descriptive statistics of the simulated asparaginase activity C_{max} and AUC following fifteen monthly doses of Oncaspar

Treatment	Parameter	Geometric Mean	Median	Mean	Minimum	Maximum	N
Oncaspar 2500 IU/m^2 dose	C_{max} (mIU/mL)	1519	1520	1519	1440	1617	200
	AUC (mIU*hr/L)	421000	422000	422000	405000	433000	200

Source: Tables 15 and 16, Population Pharmacokinetics Oncaspar and Calaspargase pegol Study AALL07P4.

The accumulation ratios were calculated and are summarized in the table below. The accumulation ratio was calculated by dividing the steady state parameter by the single dose parameter using the

geometric mean values of the 200 simulated study geometric means. At steady state, the accumulation ratio was approximately 1 for both C_{max} and $AUC_{(0\text{-}inf)}$.

Table 28: Accumulation of asparaginase activity at steady-state

Treatment	C_{max} (mIU/mL)			AUC (mIU*hr/L)		
	Geometric Mean (ss)	Geometric Mean (sd)	Accumulation Ratio	Geometric Mean (ss)	Geometric Mean (sd)	Accumulation Ratio
Oncaspar 2500 IU/m^2 dose	1519	1454	1.0	421000	391000	1

ss: steady-state; sd: single dose; accumulation ratio = $AUC_{(0\text{-}inf)}$ss/ AUC(0-inf)sd

Population PK analysis showed that children and adolescents exhibited a significantly lower volume of distribution normalized to BSA when compared to adults (1.05 vs 2.94 L/m^2). On the other hand, the volume of distribution normalized to BSA remains stable for adults up to about 80 years of age.

Intra- and inter-individual variability

Inter-subject variability of PK parameters was large, including variability due to the differences between hypersensitive and non-hypersensitive patients. The CVs (%) found by parameters throughout the clinical studies were:

- T1/2: between 14.3% and 98.5% (excluding the extremely high CV at induction in study CCG-1962 due to an outlier, already discussed),
- AUC: between 22.2% and 120.2%,
- Cmax: between 19.7% and 62.1%.

Pharmacokinetic interaction studies

- No specific pharmacokinetic drug-interaction studies have been submitted (see clinical pharmacology discussion).

Special populations

All studies mentioned in the PK section included children, except ASP-001. No PK data was provided in elderly.

2.4.3. Pharmacodynamics

Mechanism of action

No studies were submitted on the mechanism of action (see clinical pharmacology discussion).

Primary and Secondary pharmacology

Primary pharmacology

Pharmacodynamic data are presented and discussed under the clinical efficacy section.

Secondary pharmacology

Leukaemic cell kill

The *in vivo* early leukaemic cell kill using different formulation of L-asparaginase in children with newly-diagnosed ALL was determined in Study ASP-301 by the use of rhodamine-123 (RH-123). The results are shown in the following table.

Table 29: Rhodamine-123 in vivo cell kill

Treatment group	No. of patients	Mean % lymphoblasts pretreatment Mean ± SD	Decrease in mean % lymphoblasts at day 5 Mean ± SD
Oncaspar (2,500 IU/m^2)	21	79.0 ± 11.0	55.7 ± 10.2
E. coli L-asparaginase (25,000 IU/m^2)	28	84.9 ± 5.9	57.8 ± 10.1
Erwinia L-asparaginase (25,000 IU/m^2)	19	78.7 ± 7.2	57.9 ± 13.8
p-value among groups		0.02	0.73

Source: Legacy Summaries of Efficacy and Safety page 34

Pharmacodynamic interactions

- Methotrexate

Study ASP 102 investigated the use of sequential methotrexate and native L-asparaginase. The antitumor activity of the combination of methotrexate and native L-asparaginase was dose dependent. Pharmacokinetics synergy occurred when native L-asparaginase is administered 24 hours after methotrexate.

No studies have been submitted to determine the safety and optimal dose of methotrexate in combination with PEG-asparaginase.

Additional analysis: PK/PD comparison between the Supplier L and Supplier M product

A PK/PD analysis is ongoing to assess the PK comparability between the Supplier L and Supplier M product, among other objectives. Details regarding the PK/PD analysis are reported hereafter.

Objectives

This analysis is conducted in three parts: an assessment of the PK, an assessment of PD and an assessment of the immunogenicity.

Study used in the analysis

Details of the studies used to develop the PK model in this analysis are provided in the below table. All studies were open label clinical trials.

Table 30: List of studies included in the PK/PD analysis

STUDY	Subjects (n)	Product (PROD)	Formulation (FORM)	Dose (IU/m^2)	Dose Regimen	Average PK samples /patient	Average PD samples /patient
CCG-1962	60	ASN		6000	Induction	6.1	8.2
	59	PEG-ASN	Merck	2500	Delayed Intensification 1 Delayed Intensification 2	6.8	8.4
AALL07P4	50	PEG-ASN	Merck	2500	Induction Extended Induction (if applicable) Consolidation	12.2	2.2
Dana Farber	39	PEG-ASN	Lonza	2500	Induction Consolidation	13.9	0

Datasets

Study data which are utilized in the PK analysis include dosing histories (amounts, frequencies, dates and times of dosing), ASN activity (PK) and ASP (PD) with corresponding sample collection dates and times, demographic descriptors and laboratory values.

Pharmacokinetic Model Database

In order to examine potential PK differences between native ASN and PEG-ASN, the PK data obtained from study CCG-1962 which evaluated both types of ASN are used. In order to examine potential PK differences between Supplier M and Supplier L formulations of PEG-ASN, the PK data obtained from Study AALL07P4 (Supplier M formulation) and the Dana Farber study (Supplier L) formulation are used.

Pharmacokinetic Pharmacodynamic Model Database

In order to examine potential PKPD differences between native ASN and PEG-ASN, the PK and PD data obtained from study CCG-1962 which evaluated both types of ASN are used. PK and PD data from Study AALL07P4 may be used to supplement if needed.

Immunogenicity Model Database

In order to examine potential differences in the immunogenicity between native ASN and PEG-ASN, immunogenicity data obtained from study CCG-1962 which evaluated both types of ASN are used. In order to examine potential immunogenicity differences between Supplier M and Supplier L formulations of PEG-ASN, the PK data obtained from Study AALL07P4 (Supplier M formulation) and the Dana Farber study (Supplier L) formulation are used.

Patient Descriptors and Laboratory Data

Selected covariates are evaluated as possible predictors for the population PK and PK/PD models.

Table 31: Summary of Continuous Covariates and Data Items

Covariate	Description	Units
AGE	Age	years
WT	Body weight	kg
BSA	Body Surface Area	m^2
BILI	Bilirubin	mg/dL

Table 32: Summary of Categorical Covariates and Data Items

Covariate	Description	Categories
SEX	Sex	1 = Male 2 = Female
RACE	Race	1 = White 2 = Black 3 = Oriental 4 = Hispanic 5 = Native American 6 = Other/Filipino
FORM	Formulation[a]	1 = Merck 2=Lonza
PROD	Native or PEG[b]	1=native 2=PEG

Note – not all studies have all covariate information available. [a]Only Study CCG-1962 collected data from the native ASN product. [b]Only the Dana Farber study collected data using the Lonza formulation of PEG-ASN.

Interim results were provided and showed there were no differences in the asparaginase activity between the Supplier M and versions of Oncaspar. This was demonstrated graphically and by single covariate models that showed a decrease in the objective function of <3.5 points. Total bilirubin concentration was found to be a predictor of central volume of distribution (V1), increasing bilirubin concentration resulted in larger V1. BSA is a predictor of V1 and Vmax. Covariate evaluation of the model showed that gender and race did not affect PK parameters. Immunogenicity status was not associated with changes in asparaginase activity.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile of Oncaspar was assessed in patients with ALL or other haematological malignancies. Analytical validation reports were provided with satisfactory results taking into account the dates of the studies, except for some validation reports missing. General methods have been applied and considered acceptable for PK parameters calculation and statistical analyses.

The distribution volume was in the range of the estimated plasma volume. After a one-hour intravenous infusion, asparaginase activity was detected for at least 15 days after the first treatment with Oncaspar (see SmPC section 5.2).

In adults with leukaemia, the initial enzymatic activity after intravenous adminstration of Oncaspar was proportional to the dose. The elimination half-life from the plasma was between 1 and 6 days and appeared to be unaffected by the dose. It was also independent of age, sex, body surface area, renal and hepatic function, diagnosis and severity of the illness. However, terminal half-life was shorter in hypersensitive patients than in non-hypersensitive patients, and may be decreased due to the formation of high levels of anti-drug antibodies (see SmPC section 5.2). Oncaspar had a terminal half-life shorter in high antibody level patients than in low-antibody-level patients.

Results from population PK analysis and simulations suggested that asparaginase activity after 2500 IU/m^2 Oncaspar administration every 28 days, as during consolidation therapy in the newly diagnosed high risk ALL population, underwent minimal and negligible accumulation. With a dosing scheme of an injection every 14 day, accumulation is expected in patients where the terminal half-life is the longest, i.e. non-hypersensitive low-antibody level patients.

Pharmacokinetic parameters showed a rather large inter-subject variability, including variability between hypersensitive and non-hypersensitive patients. Intra-subject variability was moderate.

L-asparaginase half-life after administration of Oncaspar was found to be statistically different from the half-life after administration of Elspar or Erwiniase. Patients with newly diagnosed ALL received a single intramuscular injection of Oncaspar (2500 U/m² body surface area) or native asparaginase from E. coli (25000 U/m² body surface area) or from Erwinia (25000 U/m² body surface area). The plasma elimination half-life of Oncaspar was statistically significantly longer (5.7 days) than the plasma elimination half-lives of the native asparaginases from E. coli (1.3 days) and Erwinia (0.65 days). The immediate cell death of leukaemic cells *in vivo*, measured by rhodamine fluorescence, was the same for all three L-asparaginase preparations (see SmPC section 5.2).

ALL patients with several relapses were treated either with Oncaspar or with native asparaginase from E. coli as part of an induction therapy. Oncaspar was given in a dose of 2500 U/m² body surface intramuscularly on days 1 and 15 of induction. The mean plasma half-life of Oncaspar was 8 days in non- hypersensitive patients (AUC 10.35 U/ml/day), and 2.7 days in hypersensitive patients (AUC 3.52 U/ml/day) (see SmPC section 5.2).

There were no human mass-balance studies. However, as stated in the guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004), mass-balance studies for therapeutic proteins are not useful for determining the excretion pattern of the drug. There was no excretion of oncaspar in urine. This is consistent with the fact that pegaspargase is a protein with a high molecular weight. No change of pharmacokinetic of Oncaspar in patients with renal impairment is foreseen and thus no dose adjustment is necessary in patients with renal impairment (see SmPC sections 4.2 and 5.2).

Reduced hepatic function may decrease the lack of elimination of a protein for which hepatic degradation is an important pathway, such as Pegaspargase. While the exact role of the liver in the metabolism of asparaginase is unknown, there is no realistic scope for decreases in liver function to present clinically relevant problems in the use of Oncaspar. Since the proteolytic enzymes responsible for oncaspar metabolism are ubiquitously distributed in tissues the exact role of the liver is unknown. However any decrease in liver function is not expected to present clinical relevant problems in the use of Oncaspar. No dose adjustment is necessary in patients with hepatic impairment (see SmPC sections 4.2 and 5.2).

No impact of genetic polymorphism is expected.

There was little documentation about the influence of gender and race on pegaspargase pharmacokinetics. No effect was seen in the only study it was studied, and no effect is foreseen.

Posology of pegaspargase is already dependant on body surface area (BSA). No other investigation on the effect of weight was performed or needed.

The incidence of ALL by age has a bimodal distribution, with peaks around 2-3 years of age and 50 years of age, therefore knowledge of those two special populations is crucial. The pharmacokinetic part of this application comes in vast majority from a paediatric or teenager population, in consequence, PK was mostly documented in children. The recommended posology is 82.5 IU/kg body weight for children with a body surface area < 0.6 m². This was justified with data of previous use, and is usual in the paediatric oncology community (see also discussion on dose finding studies).

There is limited data available for patients older than 65 years. There is no PK data available for elderly patients (see SmPC section 5.2 and RMP).

Population PK analysis showed that children and adolescents exhibited a significantly lower volume of distribution normalized to BSA when compared to adults (1.05 vs 2.94 L/m^2). On the other hand, the volume of distribution normalized to BSA remained stable for adults up to about 80 years of age. Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2000 U/m^2 every 14 days (see SmPC section 4.2).

Regarding pharmacodynamic effects, pharmacodynamics was assessed in Study 1 in 57 newly diagnosed paediatric patients with standard-risk ALL who received three intramuscular doses of Oncaspar (2500 Units/m^2), one each during induction and two delayed intensification treatment phases. Pharmacodynamic activity was assessed through serial measurements of asparagine in sera (n=57) and cerebrospinal fluid (CSF) (n=50) (see SmPC section 5.1). The results are presented and discussed under clinical efficacy.

No formal analysis of drug interactions occurring in the clinical trial program was submitted. Furthermore, no clinical pharmacology studies which formally investigated drug-drug interaction potential was submitted. There is no potential for drug-food interaction known. Potential interactions that are well known for asparaginase are further discussed below and reflected accordingly in section 4.5 of the SmPC and in the Risk Management plan.

The decrease in serum proteins caused by Oncaspar can increase the toxicity of other medicinal products that are protein bound.

In addition, by inhibiting protein synthesis and cell division, Oncaspar can disturb the mechanism of action of other substances which require cell division for their effect, e.g. methotrexate.

Methotrexate and cytarabine can interfere differently: prior administration of these substances can increase the action of Oncaspar synergistically. If these substances are given subsequently, the effect of Oncaspar can be weakened antagonistically.

Oncaspar can interfere with enzymatic detoxification of other medicinal products, especially in the liver.

The use of Oncaspar can lead to fluctuating coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when anticoagulants such as coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory drugs are given concomitantly.

When glucocorticoids (e.g. prednisone) and Oncaspar are given at the same time, alterations in coagulation parameters (e.g. fall in fibrinogen and Antithrombin III deficiency, ATIII) can be more pronounced.

Immediately preceding or simultaneous treatment with vincristine can increase the toxicity of Oncaspar and increases the risk of anaphylactic reactions. Therefore, vincristine should be given in a timely manner before administration of Oncaspar in order to minimise toxicity.

An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the combination of Oncaspar with oral contraception is not recommended. Another method than oral contraception shoud be used in women of childebearing potential (see sections 4.4 and 4.6).

Simultaneous vaccination with live vaccines increases the risk of severe infections attributable to the immunosuppressive activity of Oncaspar and overall situation taking into account the underlying disease and the usually combined chemotherapy (see section 4.4). Vaccination with live vaccines should therefore be given 3 months at the earliest after termination of the entire antileukaemic treatment.

De-PEGylation occurs over the course of PEG-ASP (Oncaspar) drug storage due to hydrolytic cleavage of the labile ester bond on the succinimidyl succinate polyethylene glycol (SS-PEG) linker. The drug product shelf life is limited to 8 months (see section on quality). An analysis was performed in Study AALL07P4 to determine whether there is a relationship between drug age at induction and clinical outcomes (data not shown). Since no assay was performed during stability studies, data on the extent of protein PEGylation at the time of dosing in study AALL07P4 are not

available. However, indirect data on the extent of de-PEGylation could be obtained considering the difference between total free PEG measured at batch release and during the stability study. Overall, the provided data do not suggest any significant relationship between de-PEGylation and clinical outcomes, especially considering the proposed 8-month shelf-life.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data are considered sufficient and have been adequately reflected in the product information.

2.5. Clinical efficacy

2.5.1. Dose response studies

Oncaspar dosing and scheduling were first investigated in two studies (ASP-001 and ASP-102), in which, overall, a dose range of 500-8000 IU/m^2 IV every 14 days was administered.

ASP-001 was a phase I-II trial, conducted from 1984 to 1986 in order to evaluate the clinical pharmacology and efficacy of PEG-ASNase in malignant hematologic disorders, using an open-label, ascending multiple dose design. Cohorts of 3 patients were entered at each dose level, starting at 500 IU/m^2, which was conservative based on non-clinical data with PEG-ASNase and clinical experience with native ASNase, with subsequent cohorts at higher doses until dose-limiting toxicity was observed. Dose was also escalated in individual patients until a biological effect or a dose-limiting toxicity was observed. In total, 37 heavily pre-treated patients were enrolled and the distribution of first and final PEG-ASNase doses in the study is reported in the table below.

Table 37: First and last Oncaspar dose levels – study ASP-001

	Oncaspar dose (IU/m^2)						
	250	500	1,000	2,000	2,500	4,000	8,000
First Oncaspar dose (n)	0	5	6	7	1	5	13
Final Oncaspar dose (n)	1	1	4	9	1	8	13

A preliminary assessment of efficacy showed 3 CR (1 ALL patient, 2 NHL patients) and 2 SD (1 myeloma patient and 1 ALL patient).

ASP-102 was a phase I, open-label, non-comparative trial conducted from 1987 to 1988 in patients with refractory solid tumours and lymphomas designed to investigate the maximally tolerated dose of Methotrexate when followed by PEG-ASNase, to determine a suitable PEG-ASNase dose for Phase II studies and to assess its activity. Five cohorts of 3 patients each were to be treated with ascending doses of Methotrexate (4 administrations every 6 hours), followed within 24 hours by an IM administration of 2.000 IU/m^2 PEG-ASNase (subsequently reduced at 1.000 IU/m^2 due to toxicity). The study accrued 11 patients, including 6 patients with breast cancer and 1 each with sarcoma of the spinal cord, common bile duct cancer, rectal cancer, ovarian cancer and NHL. Nine of the 11 patients were evaluated for clinical response. Five of them (56%) exhibited stable disease and 4 (44%) had progressive disease. Methotrexate was tolerated at doses ranging from 40 to 60

mg/m^2 when followed within 24 hours by 1,000 IU/m^2 of Oncaspar. The maximum tolerated dose for Methotrexate when followed by 1,000 IU/m^2 of Oncaspar was observed at 60 mg/m^2.

Dose information from other studies

In all the pivotal studies supporting the first-line indication (CCG-1961, CCG-1962, DFCI-87-001 and DFCI-91-01) PEG-ASNase was administered at the dose of 2.500 UI/m^2 IM as single injection or every 2 weeks. The actual timing of administration differed widely between studies since PEG-ASNase was just a single component of complex multidrug treatments.

In the eight studies supporting the second-line indication, also including non-hypersensitive patients, PEG-ASNase was mainly administered at 2.000 – 2.500 IU/m^2 IM every 2 weeks.

Clinical response rates were higher at 2,000 IU/m^2 in comparison to 2,500 IU/m^2. However, the majority of data relating to the 2,000 IU/m^2 dose (n=32 out of 51) came from Study ASP-001C/003C in which PEG-ASNase could be given up to once weekly as opposed to every 2 weeks. Therefore, while the single actual dose administered may have been lower, the absolute amount of drug received during all the study period might have even exceeded that administered in most studies where PEG-ASNase was used at the dose of 2,500 IU/m^2 every 2 weeks.

2.5.2. Main studies

The efficacy data are presented for the first line indication, i.e. newly diagnosed patients never treated for their disease and second line indication, i.e. patients with one relapse/treatment failure, separately.

First-line indication

The efficacy results of four clinical trials (CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01) were submitted by the Applicant in support of the PEG-ASNase administration in first-line indication.

Study CCG-1961: Treatment of patients with acute lymphoblastic leukaemia with unfavourable features: A Phase III Group-wide Study.

CCG-1961 was submitted in the format of bibliographical references:

Grigoryan et al (2004): this publication reports on changes of amino acid serum levels in response to asparaginase therapy. Samples were collected from 1001 patients but only a subset of 73 patients was randomly selected for analysis. No clinical efficacy endpoint data were reported.

Panosyan et al (2004): the authors investigated anti-asparaginase antibodies and asparaginase enzymatic activity in the sera of 1001 patients. They presented an interim analysis of 280 patients followed for 30 months showing an association between antibody positivity and an increased rate of events.

Seibel et al (2008): In this report 1299 patients with marrow blasts ≤25% on Day 7 of induction were defined rapid early responders (RER). These patients were randomly assigned in a 2x 2 factorial design trial to standard or longer duration post-induction intensification (PII) and to standard or increased intensity PII. The effect on EFS after 5 years was reported.

Nachman et al (2009): The authors investigated outcomes and proposed prognostic factors in a sub-population of CCG-1961 composed by 262 young adults (aged 16-21 years). EFS data following 5 years of follow-up are presented.

The following table summarises the efficacy results from study CCG-1961 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of efficacy for trial CCG-1961

Title: Treatment of Patients With Acute Lymphoblastic Leukemia With Unfavourable Features: A Phase III Group-wide Study						
Study identifier	CCG-1961, NCT00002812					
Design	Interventional, open label, multicentric, partially randomized, Phase III clinical trial investigating combination chemotherapy in treating children with ALL with unfavourable features					
	Duration of main phase:	2 years for girls, 3 years for boys				
	Duration of Run-in phase:	not applicable				
	Duration of Extension phase:	at least 5-year follow-up				
Hypothesis	Superiority of Increased (containing Oncaspar) and/or Prolonged Duration Intensification Chemotherapy over Standard Intensification Chemotherapy in Rapid Early Responder (RER) high risk ALL patients Exploratory: to investigate the addition of doxorubicin vs idarubicin and cyclophosphamide to Intensification chemotherapy in Slow Early Responder (SER) patients Exploratory: to assess the impact of day 7 bone marrow status on outcome					
Seibel et. Al (2008)	Survival analysis in rapid early responder (RER) children and adolescents with high risk ALL					
Treatments groups	All RER patients		RER patients treated across all arms			
	SPII patients		RER patients treated with standard intensity chemotherapy (no Oncaspar)			
	IPII patients		RER patients treated with increased intensity chemotherapy (Oncaspar)			
	SDPII patients		RERs patients treated with standard duration chemotherapy (326 treated with Oncaspar)			
	IDPII patients		RERs patients treated with increased duration chemotherapy (324 treated with Oncaspar)			
Endpoints and definitions	Primary endpoint	EFS	EFS was calculated from time of randomization. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first			
	Co-Primary endpoint	OS	OS was calculated from time of randomization. Event considered is death for all causes			
Date of Publication	March 01, 2008					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to treat population at the time of submission for publication (February 2007)					
Descriptive statistics and estimate variability	Treatment group	All RERs	SPII	IPII	SDPII	IDPII
	Number of subjects	1299	649	650	651	648
	5-yr EFS (%)	75.5%	71.7%	81.2%	76.0%	76.8%
	± SD (%)	1.8%	2.7%	2.4%	2.6%	2.6%
	5-yr OS (%)	84.7%	83.4%	88.7%	na	na
	± SD (%)	1.5%	2.2%	1.9%	na	na
Effect estimate per comparison	Primary endpoint: 5-yr EFS	Comparison groups	SPII vs IPII			
		Relative Hazard Rate (RHR) for event	**1.61**			
		P-value	P<0.001			

		Comparison groups	SDPII vs IDPII
		Relative Hazard Rate (RHR) for event	1
		P-value	P<0.94
	Primary endpoint: 5-yr OS	Comparison groups	SPII vs IPII
		Relative Hazard Rate (RHR) for event	**1.56**
		P-value	P<0.005
Notes	na: not available		
Analysis description	**Analysis in other relevant publications**		
Nachman et al (2009)	Survival analysis in rapid early responder (RER) and slow early responder (SER) young adults (YA: 16 to 21 years) with high risk ALL		
Treatments groups	All YA patients	Young adult patients treated across all arms	
	YA SPII patients	Young adult RER patients treated with standard intensity chemotherapy (no Oncaspar)	
	YA IPII patients	Young adult RER patients treated with increased intensity chemotherapy (Oncaspar)	
	YA SDPII patients	Young adult RERs patients treated with standard duration chemotherapy (including patients treated with Oncaspar)	
	YA IDPII patients	Young adult RERs patients treated with increased duration chemotherapy (including patients treated with Oncaspar)	
	All YA SER patients	All young adult SER patients	
Endpoints and definitions	Primary endpoint	EFS was calculated from time of randomization. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first	
	Primary endpoint	OS was calculated from time of randomization. Event considered is death for all causes	
Date of Publication	November 01, 2009		

Results and Analysis

Analysis population and time point description	Intent to treat population in the YA subset of patients at the time of data cut-off (May 2006)						
Descriptive statistics and estimate variability	Treatment group	All YA	YA SPII	YA IPII	YA SDPII	YA IDPII	YA SER
	Number of subjects	262	77	88	na	na	53
	5-yr EFS (%)	71.5%	66.9%	81.8%	71.7%	77.1%	70.7%
	± SD (%)	3.6%	6.7%	5.4%	na	na	7.3%
	5-yr OS (%)	77.5%	75.6%	83.2%	na	na	na
	± SD (%)	3.3%	7.7%	6.8%	na	na	na

Effect estimate per comparison	Primary endpoint: 5-yr EFS	Comparison groups	YA SPII vs YA IPII
		P-value	P=0.07
		Comparison groups	YA SDPII vs YA IDPII
		P-value	P=0.48
	Primary endpoint: 5-yr OS	Comparison groups	YA SPII vs YA IPII
		P-value	P=0.14

Notes	na: not available				
Panosyan et al (2004)	Anti-asparaginase antibody status and clinical outcome				
Treatments groups	Group A	Patients with no sign of clinical allergies after exposure to native E.coli L-Asparaginase and with a persistent antibody-negative status			
	Group B	Patients who developed mild allergy symptoms but were persistently antibody-negative			
	Group C	Patients who developed clinically significant allergic symptoms and were antibody-positive			
	Group D	Patients with no clinical signs of hypersensitivity but with anti-asparaginase antibodies (silent inactivation)			
Endpoints and definitions	Primary endpoint	Events/patients rates during a 30-month follow-up. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first			
Date of Publication	April 01, 2004				
Results and Analysis					
Analysis population and time point description	Intent to treat population in the YA subset of patients at the time of data cut-off (May 2006)				
Descriptive statistics and estimate variability	Treatment group	Group A	Group B	Group C	Group D
	Number of subjects (%)	57 (20%)	27 (10%)	115 (41%)	81 (29%)
	30-month Events/Patients rate	3/57	2/27	3/115	13/81

Effect estimate per comparison	Primary endpoint: 30-month Events/Patients rate	Comparison groups	Group A vs all Groups
		Hazard Ratio Observed	1
		Hazard Ratio Expected	0.66
		P-value	NS
		Comparison groups	Group B vs all Groups
		Hazard Ratio Observed	1.3
		Hazard Ratio Expected	0.86
		P-value	NS
		Comparison groups	Group C vs all Groups
		Hazard Ratio Observed	0.6
		Hazard Ratio Expected	0.38
		P-value	NS
		Comparison groups	Group D vs all Groups
		Hazard Ratio Observed	3.2
		Hazard Ratio Expected	2.11
		P-value	P=0.01
Notes	Patients in Group B and C were treated with Erwinia asparaginase after clinical allergy symptoms appeared in order to continue chemotherapy according to the protocol.		

With respect to data from Panosyan et al., 61% of patients after exposure to native E.coli L-asparaginase in induction showed at least one anti-asparaginase antibody positivity throughout all the treatment, while 39% had persistently no detectable antibodies. Once high-titre Ab-positivity appeared, generally it persisted throughout the all the treatment.

The table below presents the Ab-positive ratio values over negative control per phase of treatment.

Table 39: Average antibody titers over negative control per treatment phase for antibody positive patients

Pre-Tx	Consolidation	IM1	DI1	IM2	DI2
0.99 ± 0.18	8.48 ± 87.4	36.62 ± 108.7	33.51 ± 123.3	17.5 ± 55.18	20.85 ± 78.2

Data are given as mean ± SDEV.

No anticipated asparaginase activity was detected in 81 of 88 Ab-positive patients (thus, 94% neutralizing activity). The largest subset of patients developed anti-asparaginase antibody positivity and had obvious clinical allergy symptoms (115/280; 41%). These patients were switched to Erwinia asparaginase, which did not cross-react with anti-E. coli asparaginase antibody. In patients with no clinical signs of hypersensitivity and therefore not switched to Erwinia asparaginase), but with an anti-asparaginase antibody-positive status (81/280; 29%), the presence of antibodies reduced or completely negated asparaginase enzymatic activity.

Study CCG-1962: A Randomised comparison of PEG-L-Asparaginase and Native E. coli Asparaginase in the standard treatment arm of CCG-1952 for standard-risk acute lymphoblastic leukaemia, a Phase II Limited Institution Pilot Study.

This was a multicenter, randomized study conducted as a sub-study of CCG-1952 designed to determine the safety, efficacy, and pharmacokinetics of PEG-ASNase compared with standard native ASNase as part of combination therapy in children with newly diagnosed SR-ALL.

Methods

Study Participants

Inclusion criteria:

- Newly diagnosed previously untreated ALL
- Age: 1 through 9 years, inclusive
- Initial WBC at a CCG institution: < 50,000/µL
- French American British (FAB) morphology: <= 25% L3 blasts
- Extramedullary Disease - Patients with massive lymphadenopathy, massive splenomegaly, and/or large mediastinal mass at diagnosis were eligible.
- Patients with CNS or testicular leukemia at diagnosis were eligible.
- Systemic corticosteroids given > 1 month before diagnosis, or inhalational corticosteroids given at any time will not exclude the patient.

Exclusion criteria: Corticosteroids given for > 48 hours during the month before diagnosis excluded a patient from participation in the study.

Treatments

The treatment used in the study is outlined in the table below. At the start of induction, patients were randomly assigned to receive either:

- Oncaspar (2,500 IU/m^2 i.m.) on Day 3 of Induction and Day 3 of each Delayed Intensification.
- Native *E coli* asparaginase (6,000 IU/m^2 i.m.) 3 times weekly for 9 doses during induction and for 6 doses during each delayed intensification phase.

Table 40: Treatment used in study CCG-1962

Induction	
Vincristine	i.v. 1.5 mg/m^2 days 0, 7, 14, 21
Prednisone	p.o. 40 mg/m^2 days 0-28 then 10 day taper
Pegaspargase	i.m. 2,500 IU/m^2 day 3
or Native Asparaginase	i.m. 6,000 IU/m^2 days 3, 5, 8, 10, 12, 15, 17, 19, 22
Cytarabine	i.t. 30 mg, 50 mg, or 70 mg day 0[a]
Methotrexate	i.t. 8 mg, 10 mg, or 12 mg days 7, 28[a]
Consolidation	
Vincristine	i.v. 1.5 mg/m^2 days 0, 28, 56
6-mercaptopurine	p.o. 75 mg/m^2 days 1-28
Methotrexate	i.t. 8 mg, 10 mg, or 12 mg days 7, 14, 21[a]
Interim Maintenance # 1 and # 2	
Vincristine	i.v. 1.5 mg/m^2 days 0, 28
Prednisone	p.o. 40 mg/m^2 days 0-4, 28-32
Methotrexate	p.o. 20 mg/m^2 weekly
6-mercaptopurine	p.o. 75 mg/m^2 daily
Delayed Intensification # 1 and # 2	
Vincristine	i.v. 1.5 mg/m^2 days 0, 7, 14
Dexamethasone	p.o. 10 mg/m^2 days 0-6, 14-20
Pegaspargase	i.m. 2,500 IU/m^2 day 3
Or Native Asparaginase	i.m. 6,000 IU/m^2 days 3, 5, 8, 10, 12, 15
Doxorubicin	i.v. 25 mg/m^2 days 0, 7, 14
Methotrexate	i.t. 8 mg, 10 mg, or 12 mg days 0, 28, 35[a]
Cyclophosphamide	i.v. 1,000 mg/m^2 day 28
Cytarabine	i.v. or SC 75 mg/m^2 days 29-32, 36-39
Thioguanine	p.o. 60 mg/m^2 days 28-41
Maintenance	
Vincristine	i.v. 1.5 mg/m^2 every 4 weeks
Prednisone	p.o. 40 mg/m^2 days 0-4 every 4 weeks
Methotrexate	p.o. 20 mg/m^2 weekly
6-mercaptopurine	p.o. 75 mg/m^2 daily
Methotrexate	i.t. 8 mg, 10 mg, or 12 mg every 3 months[a]

[a] The dose of intrathecal (i.t.) medications was based on age.

Source: FSR CCG-1962 Table 3 page 33

Objectives

Primary objectives:

1. To compare, in a randomised fashion, the safety of PEG-ASNase and native ASNase administered in induction and in DI phases #1 and #2 in children with newly diagnosed SR-ALL.

2. To determine, in a randomised fashion, whether the incidence of high-titer anti-ASNase antibodies in children treated with PEG-ASNase was decreased by at least 50% compared with children treated with native ASNase in DI phase #1.

Secondary objectives:

1. To determine, as a secondary endpoint, whether the incidence of high-titer anti-ASNase antibodies in children treated with PEG-ASNase was decreased by at least 50% compared with children treated with native ASNase in DI phase #2.

2. To determine the duration that serum ASNase levels remained > 0.03 IU/mL and serum ASN concentration remained < 1 µM in children treated with PEG-ASNase or native ASNase in Induction and in DI phases #1 and #2.

3. To compare pharmaco-economic data from PEG-ASNase with native ASNase in induction and both DI phases.

Outcomes / endpoints

The primary endpoint was the incidence of high-titre asparaginase antibodies in Delayed Intensification #1. The objective was to determine if a greater than 50% reduction in high-titer ASNase antibodies could be observed in PEG-ASNase compared with native ASNase in DI #1. High-titer antibody was defined as a level of antibody 2.5 times the average control level. Based on available data, the average antibody level for normal subjects and for patients before ASNase therapy was considered to be 2 U/mL, similar to that reported by Cheung et al. Consequently, high-titer antibody was defined as a level of 5 U/mL or greater and was used as the primary outcome index in the trial.

Secondary endpoints were comparison of the two treatment arms for incidence of antibodies in DI #2; ASNase activity, ASNase protein, and ASN levels in serum during Induction and DI phases; and in the CSF during Induction. Analysis of clinical outcome included response rates during Induction at Day 7 and Day 14, and end of Induction marrow examinations.

For the determination of asparaginase activity, anti-asparaginase antibodies and amino acids, blood was collected during induction Days 0, 7, 14, 21 and 28 and cerebrospinal fluid was collected during induction Days 0, 7 and 28. At least four blood samples were collected from each of 57 patients in the Oncaspar group and from 45 patients in the native *E coli* asparaginase group.

Routine physical examination and laboratory assessments were carried out at periodic intervals during the course of the trial. Bone marrow aspirates and lumbar punctures were conducted on Days 7 and 28 of Induction. Patients with blasts ≥5% on Day 7 had another bone marrow aspirate on Day 14. Bone marrow aspirates were also done at the end of Delayed Intensification #2 and at the end of Maintenance therapy.

Bone marrow responses were defined as:

- M1: <5% lymphoblasts regardless of the proportion of mature lymphocytes.
- M2: 5-25% lymphoblasts.
- M3: >25% lymphoblasts.

Remission also required normal marrow elements and cellularity.

Analysis of disease outcome (EFS) was also examined (exploratory). However, it was recognized that only large differences in this index would be detectable. Event-free survival (EFS) events included induction death, no induction response, relapse at any site, and second malignant neoplasm.

Sample size

Based on the literature, it was assumed that 50% of patients treated with native ASNase would develop ASNase antibodies during the first DI phase. The study was designed to detect a change from 50% to 25% or less in incidence of antibodies, with a power of 80% for a 1-sided hypothesis test. This led to a sample requirement of approximately 106 patients, assuming that 10% of patients might not have samples available for testing (because of early relapse or noncompliance).

Randomisation

CCG-1962 had a randomised assignment of patients to receive either PEG-ASNase or native ASNase combined with the rest of the therapy program.

Blinding (masking)

This was an open label study.

Statistical methods

For comparisons of actual values for ASNase antibodies and antibody ratio, the Wilcoxon nonparametric rank test was used.

Pharmacokinetic and pharmacodynamic analyses were conducted on the Oncaspar samples using a one-compartment open model to fit the serum asparaginase enzymatic activity and asparagine concentrations.

Kaplan-Meier estimates were used for life-table estimation, and the log-rank test was used to compare EFS outcomes. Comparisons of induction response rates and some categorical analyses of antibody ratio levels and ASNase activity groupings used exact Chi2 tests that involved global tests of differences and tests for trend (ordering) when appropriate.

Life-table comparisons of EFS outcomes for treatment regimens used intent-to-treat analyses that included all randomly assigned patients.

No specific subsets of the data were defined in the protocol for analysis. Event-free survival (EFS) was computed based on the complete data set and a subset with three patients excluded (the three patients were taken of study because of Philadelphia and ALL, parental refusal to have a second DI phase, and pancreatitis preventing ASNase treatment) and the other measures of efficacy were determined based on the availability of the required samples and analytical determinations.

Results

Participant flow

A total of 118 patients were randomized, with 59 patients assigned to each treatment arm. Twelve patients (10%) were prematurely discontinued from the study before the Maintenance phase: 5 patients (8%) who received PEG-ASNase and 7 patients (12%) who received native *E. coli* ASNase. The most frequent reason for premature discontinuation was M2 or M3 BM status: 3 patients in the native *E. coli* ASNase group and 1 patient in the PEG-ASNase group. (The location of BM status M2 or M3 is listed in the database as “other reason” for discontinuation for 4 patients.) One patient in the native *E. coli* ASNase group discontinued treatment due to grade 4 acute pancreatitis, which resulted in hospitalization and required intervention to prevent permanent impairment. The patient did not have a history of organ dysfunction.

Recruitment

The study period was May 1997 to December 2001. Nine investigators at eight investigative sites in the U.S. enrolled patients into the study.

Conduct of the study

The clinical protocol was amended on 30 December 1997 to include a pharmaco-economic analysis of the two ASNase treatments. On 20 July 1998 minor modifications to clarify BM sample collection, the toxicity definition for hyperbilirubinemia and steroid dosing were made.

Baseline data

Patient characteristics according to treatment group are summarised the table below. Patients were generally well matched and none of the characteristics was significantly different between the two groups. No patients had B-cell (L3) leukaemia. Three children had Down Syndrome and two of these were treated with Oncaspar.

Two patients were excluded from the pharmacokinetic analysis. One was Philadelphia chromosome positive (Ph+). Following Induction therapy, this patient was withdrawn from the study and given more intensive therapy. A second patient mistakenly received both native *E coli* asparaginase and Oncaspar during Induction. In accordance with the protocol, 5 children (4 randomized to native *E coli* asparaginase and 1 treated with Oncaspar) were removed from the study at the end of Induction because they had failed to achieve protocol-required bone marrow status. These children were treated with more intensive therapy than that used in the study. A total of 10 children (2 in the native *E coli* asparaginase group and 8 in the Oncaspar group) did not receive all the protocol-specified doses of asparaginase in Delayed Intensification #1 or Delayed Intensification #2 due to toxicity, protocol violation or parental choice.

Table 41: Patient characteristics by treatment assignment, study CCG-1962

Patient characteristic	PEG-ASNase n (%)	Native ASNase n (%)
Total, n	59	59
Age		
1-2 y	11 (19)	20 (34)
3-5 y	26 (44)	18 (30)
6-9 y	22 (37)	21 (36)
Sex		
Male	31 (53)	33 (56)
Female	28 (47)	26 (44)
Race		
White	38 (64)	39 (66)
Nonwhite	21 (36)	20 (34)
WBC count at diagnosis		
Below 20,000	47 (80)	46 (78)
Above 20, 000	12 (20)	13 (22)
CALLA+	50 (85)	53 (90)
Platelet count at diagnosis		
Below 50,000	20 (34)	30 (51)
50,000 to 149,000	21 (36)	19 (32)
Above 150,000	18 (30)	10 (17)
Hemoglobin (Hgb) level		
Below 8	30 (52)	24 (41)
8 - 11	22 (38)	29 (49)
Above 11	6 (10)	6 (10)
CNS disease		
> than 5 cells/µL, positive cytology	0 (0)	0 (0)
< than 5 cells/µL, positive cytology	4 (7)	9 (15)
< than 5 cells/µL, negative cytology	52 (88)	46 (78)
Mediastinal mass <than 1/3 thoracic diameter	4 (7)	6 (10)
Hepatomegaly, edge below the umbilicus	4 (7)	2 (3)
Splenomegaly, edge below the umbilicus	3 (5)	3 (5)
Lymphadenopathy, massive	1 (2)	1 (2)

CALLA+= reactive to common ALL antigen.
Source: FSR CCG-1962 Table 12 page 63

Numbers analysed

The study enrolled 118 patients. All efficacy analyses (including demographics and baseline characteristics) were based on the intent-to-treat population (as randomised).

Outcomes and estimation

Primary endpoint

At induction, the mean ± SEM anti-asparaginase antibody ratio for Oncaspar and native E.coli L-asparaginase were 1.3 ± 0.2 (n=41) and 2.3+ 0.9 (n=47) (not statistically significant), while the mean ± SEM anti-asparaginase antibody ratio in DI 1 were 1.9 ± 0.8 (n=47) for children treated with Oncaspar and 3.0 ± 0.7 (n=43) for those treated with native E.coli L-asparaginase (P=0.001 by Wilcoxon 2-sample test).

Secondary endpoints

A secondary endpoint was to show whether the same difference occurred in DI 2. The respective mean ± SEM anti-asparaginase antibody ratio for Oncaspar and native E.coli L-asparaginase in DI 2 were 2.1+0.8 (n=45) and 2.1+0.6 (n=45) (not statistically significant).

The difference in high-titer antibodies was especially evident in DI 1, in which 11/43 patients in the native E.coli ASNase arm had maximum ratios ≥ 2.5 compared with 1/47 in the PEG-ASNase arm (P=0.001, Wilcoxon test). The differences were less apparent in DI 2 (P=0.09, Wilcoxon test), and not significant during Induction (see Figure below).

The percentage of patients with an anti-asparaginase antibody ratio > 1.5, 2.0 and 2.5 were higher in the native enzyme arm both in Induction and DI 1. In DI 2 the advantage of Oncaspar over native L-asparaginase was less clear (see figure below).

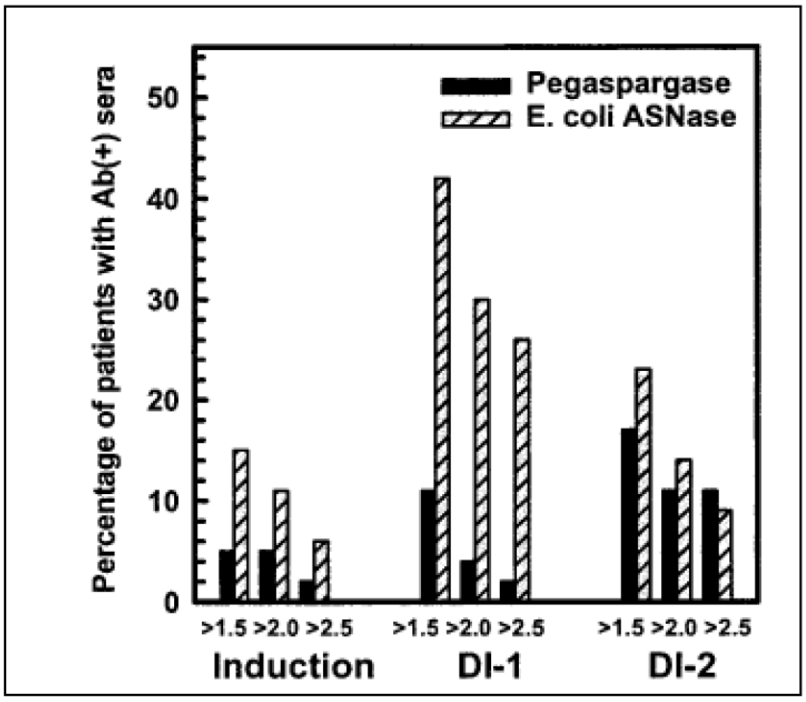

Figure 7: Percentage of patients with anti-ASNase antibody ratio over negative control > 1.5, 2.0, and 2.5 in CCG-1962

Asparaginase activity was dependent on anti-asparaginase antibody titer. Table below shows the fraction of samples collected 3 to 14 days after the start of asparaginase with asparaginase activity > 0.1 IU/mL, a level usually considered adequate to deplete blood asparagine.

Table 42: Fraction of samples with ASNase activity above 0.1 IU/mL

Antibody ratio	Induction	DI #1	DI #2
PEG-ASNase			
Below 1.5	95/98 (97%)	67/69 (97%)	63/65 (95%)
1.5-2.0	0/0	5/5 (100%)	5/5 (100%)
Above 2.0	3/3 (100%)	2/2 (100%)	9/9 (100%)
Native ASNase			
Below 1.5	79/89 (89%)	54/58 (93%)	55/59 (93%)
1.5-2.0	3/3 (100%)	4/8 (50%)	6/7 (86%)
Above 2.0	5/8 (63%)	10/20 (50%)	7/11 (64%)

Note: Native ASNase serum samples obtained Days 3-14 after the first native ASNase treatment. PEG-ASNase serum samples obtained Days 3-14 after the first PEG-ASNase treatment.

Asparagine concentrations

In all phases of treatment, serum asparagine concentrations decreased within 4 days of the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both Oncaspar and native E. coli L-asparaginase arms. Serum asparagine concentrations during the induction phase are shown in Figure 8. The patterns of serum asparagine depletion in the 2 delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase.

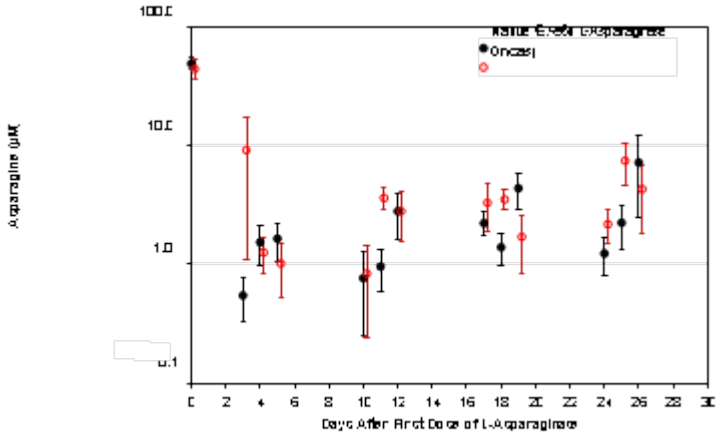

Figure 8: Mean (± standard error) serum asparagine during Study 1 induction phase

Note: Oncaspar (2500 Units/m^2 intramuscular) was administered on Day 3 of the 4-week induction phase. Native *E. coli* L-asparaginase (6000 Units/m^2 intramuscular) was administered 3 times weekly for 9 doses during induction.

CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased from a mean pre-treatment concentration of 3.1 µM to 1.7 µM on Day 4 ± 1 and 1.5 µM at 25 ± 1 days after administration of Oncaspar. These findings were similar to those observed in the native *E. coli* L-asparaginase treatment arm.

Bone marrow status

The table below presents the bone marrow status of the patients during Induction on Days 7 and 14 (or Day 28, if the Day 7 marrow status was M1).

Table 43: Bone marrow status on days 7 and 14, study CCG-1962

Bone marrow status	Oncaspar		Native E. coli asparaginase	
	Day 7	Day 14	Day 7	Day 14
M1 (<5% blasts)	36 (63%)	52 [a] (96%)	26 (47%)	43 [b] (83%)
M2 (5-25% blasts)	13 (23%)	2 (4%)	13 (24%)	5 (10%)
M3 (>25% blasts)	8 (14%)	0 (0%)	16 (29%)	4 (8%)
Total patients	57 (100%)	54 (100%)	55 (100%)	52 (100%)

[a] Includes 34 patients with M1 bone marrow status on Day 7 and Day 28 who did not have a bone marrow aspirate on Day 14.
[b] Includes 24 patients with M1 bone marrow status on Day 7 and Day 28 who did not have a bone marrow aspirate on Day 14.
Source: FSR CCG-1962 Table 14 page 67

There was statistically significantly faster clearance of lymphoblasts with Oncaspar than with native *E. coli* asparaginase. Sixteen patients (29%) in the native *E. coli* asparaginase group had M3 marrows on Day 7 compared to 8 (14%) in the Oncaspar group. All 4 patients with an M3 marrow on Day 14, which precipitated removal from the study, were in the native *E. coli* asparaginase group. At the time of the report, 7 patients had relapsed in the Oncaspar group (2x bone marrow, 3x CNS, 1x combined bone marrow and CNS plus 1 death after bone marrow relapse). This compared with 8 relapses in the native *E. coli* asparaginase group (4x bone marrow and 4 x CNS).

Event-free survival

Event-free survival rate at 3, 5 and 7 years are presented below:

	Oncaspar	native *E. coli* L-asparaginase
3-Year EFS Rate, % (95% CI)	83 (73, 93)	79 (68, 90)
5-Year EFS Rate, % (95% CI)	78 (67, 88)	73 (61, 85)
7-Year EFS Rate, % (95% CI)	75 (63, 87)	66 (52, 80)

The figure below shows the Kaplan-Meier plot of EFS for all randomised patients (n=59 for Oncaspar; n=59 for native *E. coli* asparaginase).

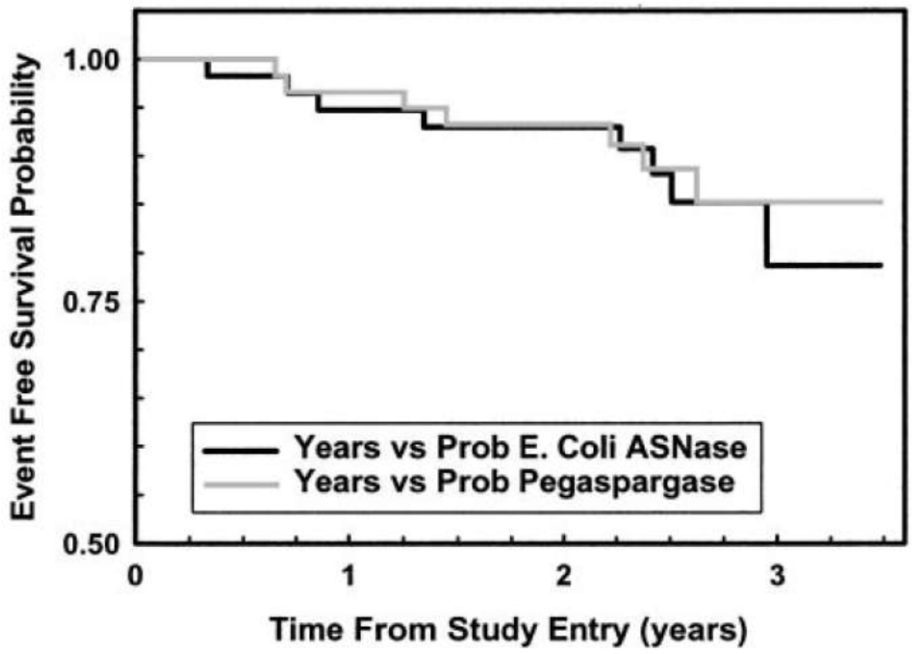

Figure 9: Kaplan-Meier Plot of Event-Free Survival (EFS) for All Randomly Assigned Patients, study CCG-1962

The following table summarises the efficacy results from study CCG-1962 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44: Summary of efficacy for trial CCG-1962

Title: A Randomized Comparison of PEG-L-Asparaginase and Native E. coli Asparaginase in the Standard Treatment Arm of CCG-1952 for Standard-Risk Acute Lymphoblastic Leukemia, A Phase II Limited Institution Pilot Study		
Study identifier	CCG-1962	
Design	Randomised, open-label, comparative study conducted as a sub-study of the CCG-1952 trial in order to investigate whether PEG-ASNase would induce lower antibody formation than native E. coli ASNase in patients naïve to any asparaginase.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	18 months not applicable at least 3-year follow-up
Hypothesis	the incidence of high-titer anti-asparaginase antibodies in children treated with Oncaspar should be decreased by at least 50% compared with children treated with native E.coli L-asparaginase in DI 1 the incidence of high-titer anti-asparaginase antibodies in children treated with Oncaspar should be decreased by at least 50% compared with children treated with native E.coli L-asparaginase in DI 2 phase the duration that serum asparaginase levels remained > 0.03 IU/mL and serum asparagine concentration remained < 1 µM in children treated with Oncaspar or native E.coli L-asparaginase in Induction and in DI 1 and DI 2 phases	
Treatments groups	Regimen N1	Patients treated with Oncaspar (2.500 IU/m^2 IM) on Day 3 of Induction and Day 3 of each DI.

	Regimen N2		Patients treated with Native E coli asparaginase (6.000 IU/m^2 IM) 3 times weekly for 9 doses during Induction and for 6 doses during each DI phase.
Endpoints and definitions	Primary endpoint	EFS	Events included: induction death, no induction response, relapse at any site, and second malignant neoplasm.
	Co-Primary endpoint	Anti-asparaginase antibody ratio	High-titer antibody was defined as a level of antibody 2.5 times the average control level. The average antibody level for normal subjects and for patients before any asparaginase therapy is 2 U/mL, consequently, high-titer antibody was defined as a level of 5 U/mL or greater and was used as the primary outcome index in the trial
Database lock	December 2001		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population			
Descriptive statistics, estimate variability and effect estimate per comparison	Treatment group	Regimen N1 (Oncaspar)	Regimen N2 (Native E coli asparaginase)	P-value
	Number of subjects	59	59	
	7-yr EFS (%)	75	66	P=NS
	95% CI (%)	63-87	52-80	
	Anti-asparaginase antibody ratio in Induction	1.3	2.3	P=NS
	± SEM	0.2	0.9	
	Anti-asparaginase antibody ratio in DI 1	1.9	3.0	P=0.001
	± SEM	0.8	0.7	
	Anti-asparaginase antibody ratio in DI 2	2.1	2.1	P=NS
	± SEM	0.8	0.6	

Study DFCI-87-001 (ASP-301): A multicentre, randomized comparison of E. coli ASNase, Erwinia ASNase or PEG-ASNase in newly diagnosed ALL patients regardless of relapse risk status.

This was an open-label study of children with newly-diagnosed ALL. The pharmacokinetics of different asparaginase preparations was studied in a subset of the DFCI-87-001 patients (see pharmacokinetic section). The data from this sub-study are recorded as Study ASP-301 and were published as Asselin et al (1993).

The objectives of Study DFCI-87-001 were to investigate the *in vitro* and *in vivo* efficacy of a single intramuscular dose of asparaginase and to correlate it with long-term outcome.

The following table summarises the efficacy results from study DFCI-87-001 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45: Summary of efficacy for trial DFCI-87-001

Title: multicenter, randomized comparison of E. coli ASNase, Erwinia ASNase or PEG-ASNase in newly diagnosed ALL patients regardless of relapse risk status					
Study identifier	DFCI-87-001, ASP-301				
Design	Open label, multicentric, Phase III clinical trial investigating combination chemotherapy in treating children with newly diagnosed ALL and comparing E. coli ASNase, Erwinia ASNase or Oncaspar in a 5-day investigational window before treatment start.				
	Duration of main phase:	5-day investigational window			
	Duration of Run-in phase:	not available			
	Duration of Extension phase:	median follow-up 4.6 years			
Hypothesis	Efficacy equivalence between the 3 asparaginases in term of *in vitro* mean total cell kill rate, i*n vivo* reduction in absolute blast count in peripheral blood and Bone Marrow and Leukemic cell kill rate at the end of the 5-day investigational windows. Impact of the *in vitro* response on long-term outcome				
Treatments groups	native E.coli group	Patients receiving a single injection of 25.000 IU/m^2 native E.coli L-asparaginase in the investigational window.			
	Erwinia group	Patients receiving a single injection of 25.000 IU/m^2 Erwinia asparaginase in the investigational window.			
	Oncaspar group	Patients receiving a single injection of 2.500 IU/m^2 Oncaspar in the investigational window.			
	In vitro responders	Patients with an *in vitro* total cell kill rate ≥40%			
	In vitro non responders	Patients with an *in vitro* total cell kill rate <40%			
Endpoints and definitions	Primary endpoint	*In vitro* mean total cell kill rate	The percentage of total cells killed in bone marrow mononuclear cells cultured with asparaginase at concentrations of 0.0001, 0.001, 0.1, 1.0 and 10.0 IU/mL for 4-6 days		
	Co-Primary endpoint	i*n vivo* reduction (%) in PB absolute blast count	Reduction (%) in circulating blast cells at the end of the investigational window.		
	Co-Primary endpoint	*in vivo* reduction (%) in BM leukemic infiltrate	Reduction (%) in bone marrow blast cells at the end of the investigational window.		
	Co-Primary endpoint	Leukemic cell kill rate	The ratio (%) between viable leukemic cells at day 0 and at the end of the investigational window.		
	Co-Primary endpoint	Patients with Leukemic events / Patients in continuous CR	Events considered: induction failure, death or ALL relapse.		
Date of Publication	January, 1999				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Patients with available samples as to July 1991				
Descriptive statistics and estimate per	Treatment group	native E.coli	Erwinia	Oncaspar	P-value

comparison	*In vitro* mean total cell kill rate	31%	39%	36%	P=0.63
	± SE (%)	n.a.	n.a.	n.a.	
	number of subjects	20	20	20	
	In vivo reduction (%) in PB absolute blast count	89%	92%	85%	P=0.36
	± SE (%)	3.5%	2.5%	4.6%	
	number of subjects	63	54	60	
	In vivo reduction (%) in BM leukemic infiltrate	33%	29%	29%	P=0.88
	± SE (%)	5.8%	6.9%	6.6%	
	number of subjects	40	27	28	
	Leukemic cell kill rate	69%	74%	65%	P=0.88
	± SE (%)	6.0%	4.8%	7.0%	
	number of subjects	17	17	16	
	Treatment group	In vitro responders		In vitro non responders	P-value
	Patients with Leukemic events / Patients in continuous CR	1/18		9/12	P=0.0008

Study DFCI-91-01: A multicenter, randomized study with an intensified post-remission therapy substituting dexamethasone for prednisone and prolonging the ASNase intensification from 20 to 30 weeks in newly diagnosed ALL patients (Silverman et al, 2001).

The following table summarises the efficacy results from study DFCI-91-01 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 46: Summary of efficacy for trial DFCI-91-01

Title: multicenter, randomized study with an intensified post-remission therapy substituting dexamethasone for prednisone and prolonging the ASNase intensification from 20 to 30 weeks in newly diagnosed ALL patients		
Study identifier	DFCI-91-01	
Design	non-proprietary open label, randomized, multicentric, Phase III clinical trial investigating efficacy and safety of multiple variations of combination chemotherapy in treating children with newly diagnosed ALL.	
	Duration of main phase:	until 2 years from achievement of CR
	Duration of Run-in phase:	not available
	Duration of Extension phase:	median follow-up 5 years

Hypothesis	To determine whether Oncaspar was associated with decrease toxicity compared to native E.coli L-asparaginase Impact of asparaginase tollerance on long-term outcome		
Treatments groups	native E.coli group		Patients receiving 25.000 IU/m^2 native E.coli L-asparaginase (30 doses) throughout treatment phases.
	Oncaspar group		Patients receiving 2.500 IU/m^2 Oncaspar (15 doses) throughout treatment phases.
	Low asparaginase tolerance		Patients able to receive asparaginases (independently of the specific formulation) for less than 26 weeks
	Good asparaginase tolerance		Patients able to receive asparaginases (independently of the specific formulation) for at least 26 weeks
Endpoints and definitions	Primary endpoint	5-y EFS	EFS was defined as the time from complete remission to the first outcome event; induction failure and induction deaths were considered events at time zero.
Date of Publication	March, 2001		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population as to December 1995			
Descriptive statistics and estimate per comparison	Treatment group	native E.coli	Oncaspar	P-value
	number of subjects	92	106	P=0.29
	EFS (%)	84%	78%	
	± SE (%)	4%	4%	
	Treatment group	Low asparaginase tolerance	Good asparaginase tolerance	P-value
	number of subjects	43	309	P<0.01
	EFS (%)	73%	90%	
	± SE (%)	7%	2%	

Two additional studies were presented in support of the first line indication:

Study DFCI-05-001:

ALL Consortium Protocol 05-001 was a treatment protocol for newly diagnosed children with ALL. Eligible patients must be at least 1 year old, but younger than 18. This protocol implemented the intensification of treatment based on end of induction MRD, and therefore built on the findings from DFCI 95-001.

The primary objective of the study was to determine the relative toxicity, clinical efficacy and biologic efficacy of IV PEG asparaginase and IM E. coli asparaginase and was subject to monitoring by the DMC. Patients were randomized between IV PEG asparaginase and IM E. coli asparaginase to assess:

a. Efficacy (disease-free survival, overall survival)

b. Health related quality of life, focused on anxiety and pain

c. Trough serum asparaginase enzyme levels, asparagines levels and antiasparaginase antibody levels.

Between 2005 and 2010, 551 evaluable patients were eligible for study treatment, of whom 526 (95%) achieved CR. In total, 463 patients participated in the ASP randomization following the Induction phase and achievement of CR; 232 were randomized to PEG-ASP (Oncaspar) and 231 were randomized to native E. coli ASP.

In the Induction Phase (4 weeks), on Day 7, all patients received 1 dose of PEG-ASP (2500 IU/m^2) by IV infusion in the multi-agent cytotoxic regimen. Following CR, risk stratification, and randomization, all patients began 30 consecutive weeks of assigned ASP treatment within the multi-agent cytotoxic regimen beginning at Week 7 of treatment:

• Consolidation Phases (ten 3-week cycles for 30 weeks, VHR patients, for 27 weeks, SR/HR patients):

- IV infusion PEG-ASP (Oncaspar) 2500 IU/m^2 every 2 weeks or

- IM native E. coli ASP 25000 IU/m^2 weekly

• CNS therapy (3 weeks) also included

- IV infusion PEG-ASP (Oncaspar) 2500 IU/m^2 or

- IM native E. coli ASP 25000 IU/m^2 weekly doses

• Asparaginase continued through CNS phase and Consolidation phases until a total of 30 doses of native E. coli ASP (dosed 3 times every week) or 15 doses of PEG-ASP (Oncaspar) (dosed once every two weeks) were administered.

The median follow-up overall for patients remaining alive is 6.0 years (range, 0.5 to 9.2). Event-free survival (EFS or disease free survival, DFS, as appropriate for some characteristics) rates were calculated from date of registration, except for EFS by randomized arm, risk group, and end-induction minimal residual disease (MRD), which were calculated from time of randomization.

The 5-year EFS [95% CI] for all 551 patients was 85% [82-88%] and the 5-year OS was 91% [88-93%] both calculated from the date of registration. No significant differences were observed between randomization arms for DFS (p=0.58) or OS (p=0.30).

The DFS [95% CI] and OS [95% CI] for PEG-ASP (Oncaspar) vs native E. coli ASP regardless of risk group category was:

• 5-year DFS rate: PEG-ASP (Oncaspar) 90% [86-94%] versus native E. coli ASP 89% [85-93%]

• 5-year OS rate: PEG-ASP (Oncaspar) 96% [93-98%] versus native E. coli ASP 94% [89-96%]

Serum Asparaginase Activity Levels

Per protocol, asparaginase enzyme levels for native E. coli ASP and PEG-ASP (Oncaspar) were drawn at different time points as described in the study report . The majority of patients (87%) in induction had a therapeutic level (≥ 0.10 IU/mL) by day 25 in induction (or 18 days following the induction dose of PEG-ASP (Oncaspar) at 2500 IU/m^2). The number of patients achieving a therapeutic level post-induction was significantly higher for patients who received PEG-ASP (Oncaspar) (99%) compared to those who received native E. coli ASP (71%) (p<0.001).

Exploratory analysis: health related quality of life (HR-QoL)

A health related quality of life (HR-QoL) analysis was conducted in 202 children and adolescents (2-18 years old) with newly diagnosed ALL randomized to receive either IM native E. coli ASP (97

patients) weekly or IV PEG-ASP (Oncaspar) (105 patients) every other week over 30 weeks during DFCI-ALL protocol intensification therapy.

Parents and patients (when age appropriate) filled out the surveys at 3 times points: after induction but before the first dose of asparaginase in CNS (baseline), between the 10th and 15th week of Consolidation II therapy, and one year after the initial diagnosis of ALL and enrollment onto 05-001. The patient and parent were analyzed separately. The survey was a 24-item HR-QoL questionnaire to measure anxiety domains, including treatment anxiety, procedural anxiety, emotional functioning, pain/hurt, general fatigue and sleep/rest fatigue.

In parents-proxy reports for younger patients, treatment anxiety scores during asparaginase therapy were higher, indicating a better HRQoL treatment anxiety score, for parents whose children were randomized to receive PEG-ASP (Oncaspar) compared to native E. coli ASP (p=0.0242). Procedural anxiety scores were also higher for parents whose children were randomized to receive PEG-ASP (Oncaspar) compared to native E. coli ASP at baseline time point of assessment (p=0.0285) and persisted during therapy (p=0.0026).

Table 47: Parent HR-QOL proxy report summaries at each time point using all available information for randomized patients

Assessment	Time Point	IM E Coli				IV PEG				Wilcoxon
		N	Median	Mean	SD	N	Median	Mean	SD	P
Treatment Anxiety	T1	91	66.67	60.62	30	98	66.67	64.63	28.22	0.4177
	T2	90	75	70.42	25.2	86	83.33	79.07	20.56	0.0242
	T3	81	91.67	81.58	23.49	90	83.33	80.46	19.6	0.3407
Procedural Anxiety	T1	91	33.33	37.18	31.95	99	50	48.44	34.97	0.0285
	T2	90	50	45.93	30.88	86	66.67	60.27	30.43	0.0026
	T3	82	66.67	63.26	30.32	90	66.67	62.69	27.55	0.7586
Emotional Functioning	T1	91	56.25	56.34	18.98	98	56.25	59.12	22.74	0.3819
	T2	90	56.25	59.51	17.56	86	62.5	61.02	18.04	0.4911
	T3	81	62.5	65.95	19.83	90	65.63	66.6	19.77	0.8632
Pain and Hurt	T1	91	50	55.49	20.35	98	50	55.36	24.01	0.9622
	T2	90	50	49.44	22.4	86	50	51.02	23.58	0.9235
	T3	81	62.5	62.5	21.1	90	62.5	59.31	23.37	0.4104
General Fatigue	T1	91	58.33	56.43	21.02	99	54.17	55	22.85	0.5462
	T2	90	50	50.57	19.35	86	50	54.04	22.64	0.4885
	T3	82	62.5	65.95	17.66	90	62.5	62.86	18.83	0.5444
Sleep/Rest Fatigue	T1	91	58.33	57.52	21.27	99	62.5	60.24	21.02	0.4005
	T2	90	54.17	55.48	18.61	86	58.33	56.32	19.33	0.6146
	T3	82	66.67	69.5	15.97	90	66.67	64.87	18.37	0.1616

† Parent survey forms are almost identical for each age group (2-4, 5-7, 8-12, and 13-18); all are on the same scale and only 1 question changes (a little longer)

Procedural anxiety scores for patients were also higher, indicating a better HRQoL procedural anxiety score, for those randomized to receive PEG-ASP (Oncaspar) (p=0.0288) during asparaginase therapy.

Table 48: Randomized patient HR-QOL report summary at each time point using all available information

Assessment	Time Point	IM E Coli				IV PEG				Wilcoxon
		N	Median	Mean	SD	N	Median	Mean	SD	P
Treatment Anxiety	T1	50	83.33	75	27.56	49	91.67	84.52	18.94	0.1142
	T2	48	83.33	78.3	23.05	49	91.67	87.93	13.93	0.0762
	T3	51	83.33	80.88	21.88	57	87.5	83.11	21.31	0.5528
Procedural Anxiety	T1	50	66.67	61	30.47	49	66.67	65.48	30	0.4612
	T2	48	66.67	59.2	27.68	49	75	71.26	24.24	0.0288
	T3	51	75	69.12	28.93	57	75	70.47	28.52	0.7889
Emotional Functioning	T1	50	62.5	65.75	22.98	49	75	69.69	22.11	0.3714
	T2	48	62.5	60.81	23.45	49	75	69.13	20.86	0.1047
	T3	51	62.5	64.95	22.81	57	62.5	68.86	21.18	0.3723
Pain and Hurt	T1	50	75	68.75	24.12	49	75	75	20.89	0.2331
	T2	47	50	56.38	23.44	49	62.5	61.48	25.11	0.2479
	T3	51	75	70.1	23.19	57	75	68.64	23.99	0.9950
General Fatigue	T1	50	70.42	64.9	23.87	49	66.67	62.69	23.47	0.5975
	T2	48	62.5	59.22	23.35	49	58.33	59.47	19.11	0.8909
	T3	51	70.83	70.33	20.09	57	66.67	66.67	19.53	0.2879
Sleep/Rest Fatigue	T1	50	60.42	59.06	24.94	48	54.17	58.25	23.12	0.5943
	T2	48	54.17	56.42	24.67	49	50	54.68	19.94	0.7616
	T3	51	75	71.73	19.21	57	62.5	62.19	17.67	0.0049

Study AALL07P4: A Pilot Study of intravenous EZN-2285 (SC-PEG E. coli L-asparaginase, IND# 100594) or Intravenous Oncaspar in the Treatment of Patients with High-Risk Acute Lymphoblastic Leukaemia.

This study was a COG study designed for newly diagnosed patients from 1 to 30 years of age with NCI HR B-precursor ALL (HRALL).

White blood cell (WBC) criteria were a) Age 1-10 years: WBC $\geq$ 50,000/μL; b) Age 10.000-30.999 years: Any WBC; c) Prior steroid therapy: Any WBC. Patients were not allowed prior cytotoxic chemotherapy with the exception of steroids and intrathecal cytarabine. This was a controlled, randomized study comparing another PEG-ASP product, EZN-2285, versus PEG-ASP (Oncaspar) in the first line treatment of ALL.

Objectives

The primary objective of the study was to determine the pharmacokinetic comparability of EZN-2285 compared to PEG-ASP (Oncaspar) given IV during Induction and Consolidation in patients with high-risk ALL receiving augmented BFM therapy.

Some of the secondary objectives were:

- To assess event-free survival (EFS) associated with the administration of EZN-2285 given during augmented post Induction intensification therapy to patients with high-risk ALL compared to Oncaspar
- To assess the tolerability and toxicities associated with the administration of EZN-2285 given during augmented post Induction intensification therapy to patients with HR ALL compared to Oncaspar
- To assess the immunogenicity of EZN-2285 including the detection of binding and neutralizing antibodies compared to Oncaspar
- To determine the proportion of patients with an asparaginase level of at least 0.1 IU/mL and the proportion with at least 0.4 IU/mL on Days 4, 15, 22 and 29 of induction compared to Oncaspar.

A total of 166 patients were enrolled in this study, 54 patients were randomized to treatment with 2500 U/m^2 Oncaspar and 111 patients were randomized to another pegylated asparaginase product.

Treatments

Treatment of these patients included combined, effective, cytotoxic multi-agent chemotherapeutic regimens for each treatment phase in the context of current practice and institutional guidelines combined with PEG-ASP (Oncaspar) to treat HR ALL. Treatment and randomization to PEG-ASP was as follows with patients continuing to receive the randomly assigned PEG-ASP product on the same schedule used in the PC arm (prednisone during Induction therapy and escalating methotrexate without leucovorin rescue during the first Interim Maintenance) of the current COG trial for high-risk ALL, AALL0232:

• Patients were randomized in a 2:1 manner to receive 2500 IU/m^2/day EZN-2285 or 2500 IU/m^2/day PEG-ASP (Oncaspar) given by IV infusion on Day 4 of Induction. These doses were used throughout treatment.

• For some patients, Extended Induction for an additional 2 weeks was based on the Day 29 bone marrow evaluation for patients having M2 marrow or an M1 marrow with ≥ 1% MRD. Patients received the randomized PEG-ASP treatment on Day 4 of the Extended Induction

• Consolidation therapy included EZN-2285 or PEG-ASP (Oncaspar) given by IV infusion on Days 15 and 43

• Following Consolidation therapy, Interim Maintenance I and II included EZN-2285 or PEG-ASP (Oncaspar) given by IV infusion on Days 2 and 22 of each cycle

• Delayed Intensification I and II followed Interim Maintenance I and II, respectively, and included EZN-2285 or PEG-ASP (Oncaspar) given by IV infusion on Days 4 and 43

Maintenance followed the final Delayed Intensification Phase and consisted of repeated 12 week cycles. The total duration of therapy was 2 years from the start of Interim Maintenance I for female patients, and 3 years from the start of Interim Maintenance I for male patients.

The EFS and overall survival (OS) was determined by randomized treatment group.

At 3-years, the EFS and overall survival (OS) for the Oncaspar treatment arm were 85.1% [95% CI 72-92%] and 92.4% [95% CI 81-97%], respectively. Overall, in the group receiving Oncaspar, all grade of hypersensitivity was 9.8%, anaphylactic reactions was 19.6%, and pancreatitis 5.9%. Grade 3 or higher of febrile neutropenia was 37.9% (see SmPC section 5.1).

Second-line population

Study ASP-001

The objectives of this trial were to define toxicities, determine the maximum tolerated dose, evaluate the clinical pharmacology and efficacy of Oncaspar administered as a 1-hour infusion every 2 weeks. Ascending multiple doses in the range 500-8,000 IU/m^2 were administered i.v.

The patient population included 37 pre-treated patients (17 males, 20 females) aged 15-73 years with refractory haematological malignancies. The study is described and discussed under the pharmacokinetics section.

Only 1 hypersensitive ALL patient was enrolled in study ASP-001. No specific efficacy data could be inferred for the single hypersensitive patient enrolled in study ASP-001.

Study ASP-001C/003C

Study ASP-001C/003C was an open label trial of PEG-L-asparaginase in the treatment of patients in relapse with malignant hematologic disorders. Patients in relapse with ALL, acute undifferentiated leukaemia or other hematologic disorders who, in the opinion of the sponsor and the investigator, might benefit from treatment with Oncaspar, were eligible for the study.

Patients were eligible for inclusion into the study if they had one of the following: At least one relapse; Documented hypersensitivity to other forms of L-asparaginase.

Patients were excluded if they had: Severe respiratory distress; A requirement for an endotracheal tube; An intracranial haemorrhage; An active symptomatic disease of the central nervous system; Rapidly progressing fatal illnesses other than haematological malignancies.

History of prior hypersensitivity to either E.Coli and/or Erwinia L-asparaginase included local and systemic reactions ranging from grade 1 to grade 4 according to common toxicity criteria.

PEG-ASNase was administered at a dose of 2,000 IU/m^2 IM as a single agent or in combination therapy to induce remission during induction. A subsequent amendment allowed patients in CR to receive maintenance therapy, given as 2,000 IU/m^2 IM either as a single agent or in combination with other chemotherapy agents, with a dosing interval of not less than one week (as determined by the investigator) until treatment with Oncaspar was no longer considered safe or beneficial to the patient.

The study objective was to determine the efficacy and safety of Oncaspar as a single agent or in combination with other chemotherapy agents in inducing and maintaining remission in patients with refractory hematologic malignancies or in ALL patients who had known hypersensitivity to the native forms of L-asparaginase.

A total of 41 relapsed patients with a variety of haematological malignancies were enrolled, ranging from 1 to 66 years old. Thirty-four of these patients had a diagnosis of ALL, five had other leukaemias, one had testicular lymphoma and one had a cutaneous T-Cell NHL (mycosis fungoides type). Thirty of the 41 total patients (73%) were hypersensitive to native L-asparaginase. Twenty-nine of these patients had ALL and one had testicular lymphoma.

Efficacy data for 38 patients were evaluated. Three hypersensitive patients were not evaluated for efficacy. Response rates in hypersensitive patients at the end of induction are summarized in table below:

Table 49: Clinical response: hypersensitive patients in induction phase, study ASP-001C/003C

Type of therapy	n		Highest therapeutic response				
	Treated	Evaluated	Complete remission	Partial remission	Haematologic improvement	Therapeutic effect	No response
Single agent	4	4	1 (25%)	0	0	0	3 (75%)
Combined therapy	7	7	2 (29%)	1 (14%)	1 (14%)	2 (29%)	1 (14%)
Overall	11	11	3 (27%)	1 (9%)	1 (9%)	2 (18%)	4 (36%)

Source: FSR ASP-001C/003C Appendix G page iv

One hypersensitive patient out of 4 (25%) obtained a CR when PEG-ASNase was administered as single agent, while the remaining 3 hypersensitive patients had no response. When Oncaspar was

administered in combined therapy, CR was reached by 2 hypersensitive patients (29%), with 1 additional hypersensitive patient obtaining PR (14%).

Table 50: Clinical response: non-hypersensitive patients in induction phase, study ASP-001C/003C

Type of therapy	n		Highest therapeutic response				
	Treated	Evaluated	Complete remission	Partial remission	Haematologic improvement	Therapeutic effect	No response
Single agent	5	5	0	1 (20%)	1 (20%)	0	3 (60%)
Combined therapy	4	4	1 (25%)	0	1 (25%)	0	2 (50%)
Overall	9	9	1 (11%)	1 (11%)	2 (22%)	0	5 (55%)

Source: FSR ASP-001C/003C Appendix G page iv

Results in patients eligible to maintenance therapy are summarized in table below:

Table 33: Clinical response: Maintenance phase, Study ASP-001C/003C

Type of patients	n		Highest therapeutic response				
	Treated	Evaluated	Complete remission	Partial remission	Haematologic improvement	Therapeutic effect	No response
Hypersensitive (Single & combined therapies)	22	19	17 (89%)	0	0	1 (5%)	1 (5%)
Non-hypersensitive (Combined therapy)	2	2	2 (100%)	0	0	0	0
Overall	24	21	19 (90%)	0	0	1 (5%)	1 (5%)

Source: FSR ASP-001C/003C Appendix G page iv

The majority (17/19, 89%) of evaluable hypersensitive patients remain in CR during maintenance therapy with Oncaspar. A relapse occurred in 2 subjects.

Study ASP-201A: An open label multicentre study of PEG-L-asparaginase in the treatment of acute lymphocytic leukaemia or acute undifferentiated leukaemia in children.

ALL or AUL patients relapsed after exposure to native ASNase were enrolled. Nine patients with known hypersensitivity to native forms of L-asparaginase were also included.

Inclusion criteria were: Histological proof of ALL or AUL; At least one relapse; Patient entered at diagnosis of relapse; Measurable disease present; Patient classified as standard or high risk; Score of ≤ 2 on the Zubrod Scale;Patient had relapsed after exposure to native L-asparaginase.

Exclusion criteria were: Severe respiratory distress; Requirement for an endotracheal tube; Intracranial haemorrhage; Septic shock; Anaphylactic reaction to prior treatment with native L-asparaginase; Pancreatitis or history of pancreatitis; Rapidly progressing fatal illness other than haematological malignancies; History of coagulopathy; Other neoplasms (except skin non-

melanoma); Hyperuricaemia; Liver abnormalities (SGOT >200 IU/mL, SGPT >200 IU/mL); Impaired renal function (serum creatinine >2 mg% or >50 mM).

Exceptions were permitted to allow patients with known hypersensitivity to native forms of L-asparaginase to be enrolled. In addition, the protocol was amended to allow the investigator to continue treatment beyond the induction phase for any patient that was considered to have responded to the PEG-L-asparaginase treatment.

PEG-ASNase 2,000 IU/m^2 was administered once every two weeks (3 doses) during a five week induction period. Over a 14 day "investigational window" PEG-ASNase was administered as a single agent and, subsequently, in combination with Vincristine and Prednisone (standard induction agents for ALL), by intramuscular injection or 2-hour intravenous infusion at the investigator's discretion. Study protocol was amended to allow the investigator to continue treatment beyond the induction phase for any patient that was considered to have obtained a good response.

The objective of this open-label trial was to determine the efficacy and safety of Oncaspar in inducing remission in relapsed children with ALL or acute undifferentiated leukaemia (AUL) during a five week induction period.

A total of 42 relapsed patients were enrolled in this study. Diagnoses were ALL (n=37), T-cell NHL (n=2), acute non-lymphoblastic leukaemia (ANLL; n=2) and acute myelogenous leukaemia (AML; n=1). Nine of the 42 patients had known hypersensitivity to the native forms of L-ASNase prior to study enrolment, including 7 cases of ALL.

A total of 44 doses of PEG-ASNase were administered to the 9 hypersensitive patients (range 2-10 doses per patient). Response rates reported for the 9 hypersensitive patients are summarised below.

Table 34: Highest therapeutic response in hypersensitive patients, study ASP-201A

Treatment phase	N [a]		Highest therapeutic response			
	Treated	Evaluated	Complete remission	Partial remission	Haematologic improvement	No response
Induction (single agent; 14-day investigational window)	6	4	0	1 (25%)	1 (25%)	2 (50%)
Induction (combination therapy)	8	8	3 (38%)	2 (25%)	0	3 (38%)
Extension	5	5	4 (80%)	1 (20%)	0	0
Overallb	9	8	4 (50%)	1 (13%)	0	3 (37%)

[a] Not all patients were evaluated due to other agents received or absence of assessments of objective response. [b] Highest response achieved by the patient regardless of treatment phase.
Source: FSR ASP-201A page 36.

Hypersensitive patients had an overall PEG-ASNase response rate of 50% (single agent) and 63% (as part of standard combination induction therapy).

The highest therapeutic responses achieved by the non-hypersensitive patients are shown in the table below:

Table 35: Highest therapeutic response in non-hypersensitive patients, Study ASP-201A

Treatment phase	N [a]		Highest therapeutic response				
	Treated	Evaluated	Complete remission	Partial remission	Haematologic improvement	Therapeutic effect	No response
Induction (single agent; 14-day investigational window)	24	23	3 (13%)	2 (9%)	5 (22%)	3 (13%)	10 (43%)
Induction (combination therapy)	26	25	16 (64%)	3 (12%)	0	2 (8%)	4 (16%)
Extension	11	11	8 (73%)	2 (18%)	0	0	1 (9%)
Overall [b]	33	29	16 (53%)	3 (10%)	0	3 (10%)	7 (24%)

[a] Not all patients were evaluated due to other agents received or absence of assessments of objective response.
[b] Highest response achieved by the patient regardless of treatment phase.
Source: FSR ASP-201A page 37.

Overall, the non-hypersensitive patients had an Oncaspar response rate of 57% as a single agent and 84% as part of standard combination induction therapy.

Study ASP-302: Intensified therapy based on patient specific system exposure to VM-26 in children with relapsed acute lymphoblastic leukaemia.

The study had an open-label design and was conducted in 3 phases:

Phase I: Early therapy.

Phase II: Re-induction therapy.

Phase III: Remission therapy / maintenance.

The study was conducted in relapsed ALL patients. Patients were eligible for inclusion if they had evidence of bone marrow relapse during or after treatment with multi-agent rotational chemotherapy. Patients were excluded if they had a history of life-threatening sensitivity to VM-26 (teniposide). A known hypersensitivity to other (non-PEGylated) forms of L-asparaginase did not exclude a patient from participation.

PEG-ASNase 2,500 IU/m^2 was administered IM every 2 weeks during re-induction and remission therapy, for a total of 29 administrations as part of a multi-drug chemotherapy protocol. Twenty-one relapsed ALL patients were enrolled, including 4 patients hypersensitive to native ASNase.

The main purpose of this study was to obtain pharmacokinetic and long-term safety data on Oncaspar.

The study was conducted in 21 relapsed ALL patients (13 male, 8 female) ranging in age from 1 to 35 years old. Four of the male patients were known to be hypersensitive to native asparaginase prior to study participation.

The 4 hypersensitive patients received a collective total of 72 doses of Oncaspar ranging from 10 to 29 doses per patient. The 17 non-hypersensitive patients received a collective total of 107 doses of Oncaspar ranging from 2 to 15 doses per patient.

Although efficacy evaluation was not a formal objective of this study, some assessments of efficacy were anyway performed and a summary of response is shown below:

Table 54: Summary of highest objective responses, study ASP-302

Patient population	N		Highest therapeutic response			
	Treated	Evaluated	Complete remission	Partial response	Haematologic improvement	No response
Hypersensitive	4	4	4 (100%)	0	0	0
Non-hypersensitive	17	16	9 (56%)	2 (13%)	0	5 (31%)
All patients	21	20	13 (65%)	2 (10%)	0	5 (25%)

Source: FSR ASP-302 page 27.

Study ASP-304: PEG-L-asparaginase vs native-L-asparaginase in combination with standard agents as second induction therapy in children with ALL in bone marrow relapse.

Inclusion criteria: Diagnosis of ALL before age 21 years and was in the second hematological relapse; Life expectancy ≥ 4 weeks Adequate hepatic and renal function (SGPT <200 IU/L; creatinine <2 mg/dL).

Exclusion criteria were as follows: Presence of CNS disease (unless the investigator judged it appropriate to withhold intrathecal chemotherapy during the 4 weeks of Oncaspar combination chemotherapy; intrathecal medication could be given with the screening lumbar puncture at the discretion of the physician); Failure of other induction regimens which contained L-asparaginase.

Patients without a history of hypersensitivity to native (E coli or Erwinia) asparaginase were randomised to receive either PEG-ASNase 2,500 IU/m^2 IM (2 total doses: Day 1 and Day 15) or native E coli-derived ASNase 10,000 IU/m^2 IM (12 total doses: 3 times per week for 26 days). In case of known hypersensitivity to native enzyme, patients were directly assigned to treatment with PEG-ASNase.

In the PEG-ASNase arm, treatment continuation in the maintenance phase was at the physician's discretion. Patients assigned to native E.coli ASNase were also allowed to continue maintenance therapy with PEG-ASNase following a protocol amendment.

The objectives of the study were to compare the efficacy and toxicity of Oncaspar administration with that of native E coli-derived L-asparaginase when used as part of a standard combination chemotherapy re-induction regimen in children with ALL who are in second haematologic relapse. The pharmacokinetic objectives were to determine the drug half-life for each product. In addition, antibodies to L-asparaginase were monitored in all patients.

Plasma concentrations of L-asparaginase and anti-asparaginase antibody titres were ascertained prior to the administration of Oncaspar and on Days 1, 2, 3, 4, 8, 15, 22, 29 and 36. Patients were evaluated on Day 29 for evidence of clinical response and were followed to Day 36 for toxicities and adverse experiences.

Objective responses to Oncaspar were recorded on Day 35 by the investigators against the following criteria:

- Complete remission: M1 marrow (<5% blasts).
- Partial remission: M2 marrow (≥ 5 to ≤ 25% blasts).
- Minor response: A 75% decrease in circulating blasts or organomegaly, without a change in marrow status.
- Stable disease: No change in clinical or marrow status.

- No response: M3 marrow (>25% blasts), without improvement in peripheral blood counts or organomegaly.

- Progressive disease: >25% increase of blasts in the marrow or peripheral blood, or rapid and advancing organomegaly.

In addition, at each clinic visit the investigator evaluated the patient's response to treatment based upon clinical symptomatology, measurements of the liver, spleen and lymph nodes plus profiles of peripheral blood or bone marrow. Clinical and laboratory evaluations were repeated at the time of a patient's termination from the study where possible.

A total of 76 patients participated in the study (47 male, 29 female). Of these, 16 completed the trial. The remaining were terminated from the study for the following reasons: Progressive disease (n=27); Relapse (n=18); Bone marrow transplant (n=7); Death (n=4); Toxicities (n=3); Refusal of further therapy (n=1). Forty patients were directly assigned to Oncaspar treatment and 19 further patients were randomized to Oncaspar therapy. These patients received 2 doses of the drug intramuscularly at 2,500 IU/m^2 every 14 days. Seventeen patients were randomized to treatment with 10,000 IU/m^2 intramuscular native E. coli L-asparaginase (Elspar) 3 times per week for a total of 12 doses.

Demographics and baseline characteristics are presented in the table below:

Table 36: Summary of demographics and baseline characteristics

Treatment assignment	n	Mean age (years)	Mean number of relapses	Mean number of prior exposures	Mean number of induction attempts	Disease duration (months)
Oncaspar (directly assigned)	40	8.4	2.2	2.6	2.5	37.5
Oncaspar (randomised)	19	8.2	2.1	2.1	2.3	42.5
Elspar (randomised)	17	9.8	2.0	1.8	2.4	45.4
Total	**76**	**8.6**	**2.1**	**2.3**	**2.4**	**40.5**

Source: FSR ASP-304 January 14, 1994 page 25

Table 37: Exposure to study drug

Treatment assignment	n	Total collective doses	Mean number of doses per patient	Range (min - max)
Oncaspar (directly assigned)	40	79	2.0	1 - 2
Oncaspar (randomised)	19	36	1.9	1 - 2
Elspar (randomised)	17	176	10.4	4 - 12

Source: FSR ASP-304 January 14, 1994 page 27

Overall, fifty nine patients received PEG-ASNase, 40 hypersensitive patients were directly assigned to PEG-ASNase and 19 non-hypersensitive were randomly assigned to Oncaspar.

A summary of response rates is shown below:

Table 38: Induction efficacy data, study ASP-304

Patient population	N		Highest therapeutic response			
	Treated	Evaluated	Complete remission	Partial remission	No response	Combined response rate a
Oncaspar (directly assigned)	40	39	16 (41%)	5 (13%)	18 (46%)	21 (54%)
Oncaspar (randomised)	19	18	7 (39%)	3 (17%)	8 (44%)	10 (56%)
Native L-asparaginase (randomised)	17	17	8 (47%)	0	9 (53%)	8 (47%)

[a] Combined response rate = Complete remission + Partial remission.
Source: FSR ASP-304 January 14, 1994 page 35.

The ORR for the two randomized populations was similar (56% vs 47%) and the difference was not statistically significant (chi squared test, p=0.615). The rate of CR in the randomised populations was 39% vs 47% (p=0.625).

The clinical response data were summarised by Day 0 and Day 28 anti-L-asparaginase antibody levels to determine if there was a correlation and data are presented below:

Table 58: Oncaspar and Elspar clinical response data by antibody level, study ASP-304

Day 28 highest response	Day 0 antibody level		Day 28 antibody level	
	Low (N=40) n (%)	High (N=13) n (%)	Low (N=22) n (%)	High (N=31) n (%)
Complete Remission	17 (43%)	3 (23%)	11 (50%)	9 (29%)
Partial Remission	4 (10%)	3 (23%)	3 (14%)	4 (13%)
No Response	19 (48%)	7 (54%)	8 (36%)	18 (58%)
Response Rate (CR + PR)	21 (53%)	6 (46%)	14 (64%)	13 (42%)

Source: FSR ASP-304 September 15 1994, page 37

Study ASP-400: A pilot study for the evaluation of PEG-L-asparaginase in the treatment of patients in relapse with acute lymphoblastic leukaemia.

This is an open-label multicentre study. The study was conducted in Germany.

Patients were eligible as follows: Age ≤21 years; Histological proof of ALL, AUL or NHL; ≥1 relapse.

Exclusion criteria were: Age >21 years; Severe respiratory distress; Requirement for an endotracheal tube; Intracranial haemorrhage; Septic shock.

The study was divided into 3 phases:

Phase I: Induction treatment lasting 15 days in which PEG-ASNase 2,000 IU/m^2 IV was administered on Day 12. The other drugs used during this phase were cisplatin, vincristine, methotrexate and prednisone.

Phase II: Consolidation treatment C1, starting at Week 3 and lasting 7 days, in which PEG-ASNase 2,000 IU/m^2 IV was administered on Day 5. The other drugs used during this phase were methotrexate, HD Ara-C and VP-16.

Phase III: Consolidation treatment C2, starting at Week 6 and lasting 7 days, in which PEG-ASNase 2,000 IU/m^2 IV was administered on Day 5. The other drugs used during this phase were HD prednisone, DDP or ifosfamide, daunorubicin and methotrexate.

Phase II therapy was repeated on Week 9 of treatment after a bone marrow aspirate was obtained. At Week 12, if the patient achieved (or had been maintained in) CR, the possibility to perform an autologous or allogeneic bone marrow transplant was evaluated. All patients were to be terminated from the study at Week 12. The analysis comprises 44 patients, 13/44 (30%) were known to be hypersensitive to native L-ASNase. All 13 hypersensitive patients had a diagnosis of ALL.

The primary objective of this open-label multicenter study was to evaluate the safety and efficacy of Oncaspar in patients who relapsed within 15 months of diagnosis or had shown evidence of refractory disease. A secondary purpose was to induce a complete remission so that patients could qualify for autologous or allogeneic bone marrow transplantation.

A total of 51 patients were enrolled and, of these, records were available for analysis from 47 patients. Two patients were excluded from the analysis for protocol violations. In addition, one patient was enrolled twice with different investigator/patient numbers and was considered as a single patient in the data analysis. Therefore the analysis comprises 44 patients (26 males, 18 females). Thirteen of these patients (6 males, 7 females; 30% of total) were known to be hypersensitive to native L-asparaginase. All hypersensitive patients had a diagnosis of ALL.

31 of the 44 patients were not hypersensitive to native L-asparaginase and ranged in age from 2 to 18 years old. Among them, 29 had a diagnosis of ALL and 2 had a diagnosis of NHL.

The highest objective response achieved by each patient was considered the highest therapeutic response.

Table 59: Highest therapeutic response in hypersensitive patients, Study ASP-400

Patient population	n	Highest therapeutic response			
		Complete remission	Partial remission	Haematologic improvement	No response
Hypersensitive	13	6 (46%)	1 (8%)	1 (8%)	5 (38%)

Source: FSR ASP-400 page 26-27.

Table 60: Highest therapeutic response in non- hypersensitive patients, Study ASP-400

Patient population	n	Highest therapeutic response			
		Complete remission	Partial remission	Haematologic improvement	No response
Non-hypersensitive	31	21 (68%)	4 (13%)	0	6 (19%)

Source: FSR ASP-400 page 27

Clinical studies in special populations

The age distribution of hypersensitive ALL patients included in the PEG-ASNase clinical trials in the second-line population (excluding Study ASP-400) is shown below:

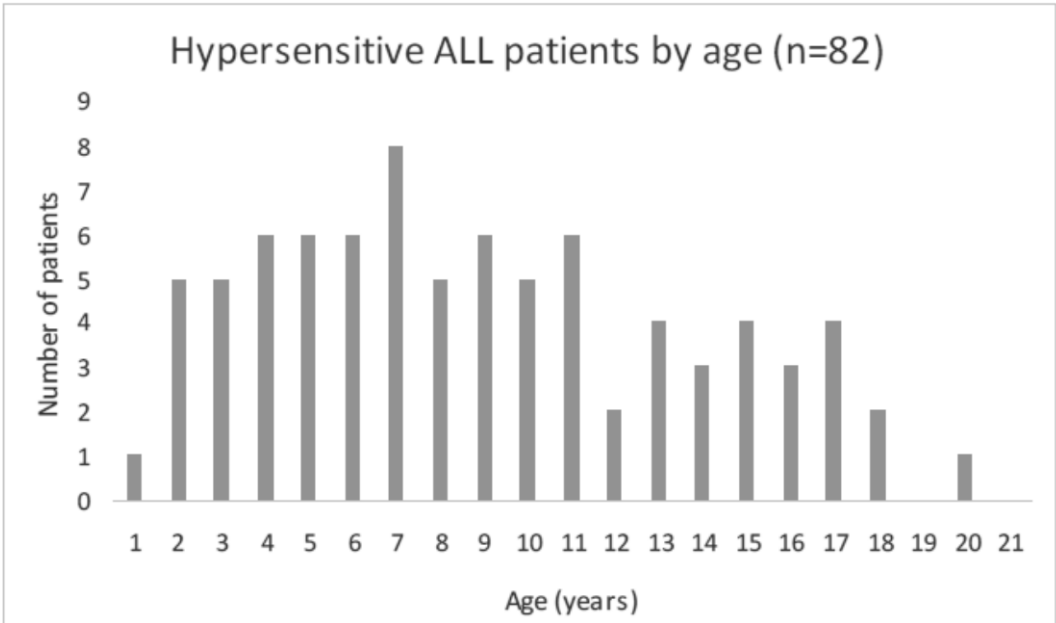

Figure 10: Age distribution of hypersensitive ALL patients studied (all Oncaspar trials; n=82)

Almost all the studied hypersensitive patients were paediatric with none being more than 20 years old. Therapeutic responses by age for hypersensitive ALL patients participating in Studies ASP-001, ASP-001C/003C, ASP-302 and ASP-304 are shown below. These data are related to 77 patients, including 51 with a clinical response (66%) and 25 patients who had no clinical response (34%).

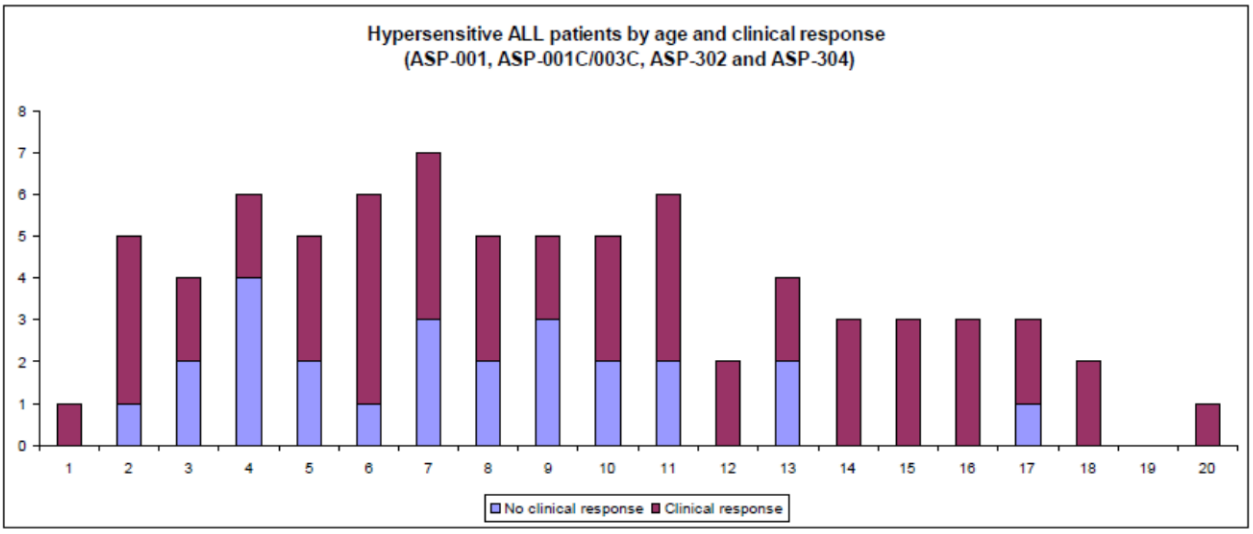

Figure 11: Hypersensitive ALL patients by age and clinical response (n=76)

The diagram shows that the pattern of response/no response is evenly distributed at least up to the early teenage years. Although the number of hypersensitive ALL patients aged ≥14 years is small (n=15), only 1 of these patients (7%) did not respond to treatment with PEG-ASNase. Twenty-five out of 43 hypersensitive ALL patients aged 1 to <10 years (58%) had a clinical response, while twenty-six out of 33 higher risk patients aged <1 year or ≥10 years (79%) had a clinical response.

With respect to non-hypersensitive patients, the four studies investigating Oncaspar use in the first-line population all reported sub-group data in slightly different ways and/or studied differing patient populations. Accordingly, direct comparison of the results in sub-populations is not possible. Table below summarises the main efficacy sub-group data from these studies.

Table 61: Subgroup analyses in clinical trials investigating first-line use of Oncaspar

Study and population studied	Reported results in sub-groups
CCG-1961 (Seibel et al, 2008). Newly-diagnosed higher-risk ALL at age 1 to 21 years.	5-year EFS: • Increased intensity therapy was better than standard intensity in B-cell ALL (80.4% vs 70.4%; p=0.001). • Increased intensity therapy was better than standard intensity in children aged 1-9 years (82.1% vs 70.8%; p=0.009). • Increased intensity therapy was better than standard intensity in patients aged >10 years (80.4% vs 72.3%; p=0.003). • Rapid early responders with presenting WBC ≥200,000/mm3 had a worse outcome than those with lower presenting WBC (60% vs 73%; p=0.008). • Rapid early responders aged 12 to <18 months of age had a worse outcome than older patients (60.2% vs 76.8%; p=0.047.
CCG-1962 (Avramis et al, 2002). Newly-diagnosed, standard risk ALL aged 1-9 years with WBC ≤50,000/µLand ≤20% surface Ig-positive leukaemic blasts.	No specific sub-group data presented.
DFCI-87-001 (Asselin et al, 1999b). Children with newly-diagnosed ALL.	Patients who are *in vitro* non-responders are at higher risk of a leukaemic event than those who were *in vitro* responders (p<0.05).
DFCI-91-01 (Silverman et al, 2001). Newly-diagnosed B-cell ALL (excluding mature B-cell disease).	• Standard risk patients had numerically better EFS, LFS and OS outcomes at 5-year follow-up. • Using CTEP risk criteria, there was no statistically significant difference in EFS, however, a numerical trend in point estimate of EFS was apparent: ○ Infants aged <1 year (71%). ○ T-cell ALL (79%). ○ High-risk B-cell ALL (82%). ○ Standard-risk B-cell ALL (85%).

Supportive studies

As supportive data a review of published literature relevant to the indication in the first-line and second line population was conducted. The searching and selection strategy resulted in the inclusion of 23 relevant publications that were covered by the analysis for the first line indication. Eighteen out of 23 publications related to children, while 6 out of 23 were relevant to adults (but 4 of the “paediatric” papers include patients up to age 21 years). Fourteen papers globally concerned newly-diagnosed patients, 1 paper concerned a pre-induction treatment window, 5 studied initial induction and 8 looked at consolidation/intensification. Eleven papers studied relapsed/refractory patients.

Four papers (Barry et al. 2007; Jarrar et al. 2006; Salzer et al. 2007; Winter et al. 2006) discussed the efficacy results from studies investigating the use of 2.500 IU/m^2 Oncaspar every 2 weeks. Efficacy results showed better responses in young, newly-diagnosed patients with ALL (Barry et al, 2007). Jarrer et al (2006), Salzer et al (2007) and Winter et al (2006) all studied higher risk

groups so the lower reported efficacy rates are to be expected. It is not possible to establish the effect of the switch from 2-weekly to 4-weekly dosing on efficacy outcomes in Winter et al (2006).

Six publications discuss the efficacy results from studies investigating the use of Oncaspar in children at doses and schedules other than 2.500 IU/m^2 every 2 weeks. Three of these (Appel et al. 2008; Sedki et al. 2008; Vora et al. 2013) concerned less intensive therapy and three look at more intensive therapy. Efficacy with reduced intensity Oncaspar treatments was good in the easier-to-treat populations (i.e. new diagnosis pre-B ALL patients and patients with low-risk disease following initial Induction therapy). Efficacy was also good in terms of re-induction in relapsed/refractory ALL (Sedki et al, 2008) although this was a very small study. Of note, the patients in this study who achieved remission underwent BMT, which made assessment of Oncaspar role in long-term outcome challenging.

Efficacy in harder-to-treat populations (i.e. pre-T ALL and BCR-ABL positive disease) was more modest. The relationship between good early clinical response (in terms of MRD) and favourable long-term outcome is confirmed. All the reported efficacy results are consistent with expectations.

With regards to the efficacy data relative to children treated with more intensive Oncaspar regimes, three studies (Raetz et al. 2008; Saarinen-Pihkala et al. 2012; Thomson et al. 2004) where more intensive Oncaspar therapy was administered were conducted in children with relapsed ALL. There was no evidence that a more intensive therapy might be beneficial in newly-diagnosed disease. All studies used Oncaspar for either 2 or 4 consecutive weeks in the context of re-Induction. There is therefore no suggestion that more intensive therapy might be beneficial over longer periods during consolidation and/or intensification. The success rate for achieving remission is consistently high (≥ 89%) except for patients with early relapse (a known poor prognostic factor). For these patients, remission achievement was 68% (Raetz et al, 2008). EFS for patients with isolated extra-medullary relapse was good (75% after 4 years), but 4-year EFS in general was much lower (49%). This is consistent with the relapsed setting. Literature data show that Oncaspar had been effectively used in every paediatric ALL setting and with variable doses and schedules of administration. Results are dependent on the population which has been investigated.

Two publications (Aguayo et al. 1999; Ayoubi et al. 2009) discussed the efficacy results from studies investigating the use of Oncaspar at the dose of 2.500 IU/m^2 every two weeks in adults. The efficacy results were disappointing, as expected given that the trial investigated a refractory/relapsed adult populations characterized by a known poor prognosis. In both studies the median duration of remission in those patients who achieved it was similar (3-4 months). Overall, the results confirmed that the prognosis for adults with relapsed ALL is weak.

Three publications (Kozlowski et al. 2012; Douer et al. 2007; Vora et al. 2013) discussed the efficacy results from studies investigating the use of Oncaspar in adults at doses and schedules other than 2.500 IU/m^2 every 2 weeks. All of these concern less intensive therapy than is proposed for marketing. Kozlowski et al (2012) studied relapsed adult patients (similar to Aguayo et al, 1999 and Ayoubi et al, 2009; see above) but with a very low Oncaspar dose (500 IU/m^2). An encouraging 63% of patients achieved remission but only 15% were still alive at 5 years. The data from Douer et al (2007) showed that Oncaspar is efficacious in inducing remission in newly-diagnosed adult patients. The dose used was slightly lower than is proposed for marketing (2.000 IU/m^2 vs 2.500 IU/m^2). Remission was achieved in 96% of cases, which is comparable to the remission rate seen in children. Unfortunately, relapse rate and overall survival are much worse than is the case for children. The Study by Vora et al (2013) was large, but only a small subset of patients (n=20) were aged ≥ 16 years and none was aged >25 years. Furthermore, the patients were treated according to paediatric oncology approaches. The inclusion of this trial under “adults” here is therefore dictated by the conventional approach to age categorization rather than by the philosophy of the study. Detailed efficacy outcomes for the “adult” sub-group are not reported. A hazard ratio for older age with relatively narrow confidence intervals was obtained from so few

older patients. All three publications concern less intensive Oncaspar therapy; more intensive use has not been investigated despite the relatively poor outcomes for adults with ALL.

Complete remission rates and OS outcomes across publications are very heterogeneous, confirming the scarce information about the use of Oncaspar in adult patients, especially in the first-line setting.

Regarding publications relevant to the indication in the Second-Line Population, a relative small number of literature papers about Oncaspar administration have been produced as compared to first-line patients. In the publication of Kurtzberg et al. in both the Oncaspar directly assigned and the Oncaspar randomized group, when a high titre of anti-asparaginase antibodies was detected, CR rates dropped from 75-85% to 40%. The importance of anti-asparaginase antibody status in second-line patients treated with Oncaspar is therefore confirmed.Abishire et al. (2000) investigated every week vs 2-weekly administration of Oncaspar (2.500 IU/m^2) in relapsed ALL patients. Weekly Oncaspar in hypersensitive patients conferred a 7-fold decrease in risk of induction failure (OR 0.13, 95%CI 0.028-0.599).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The sources of native *E. coli* L-asparaginase drug substance used in the manufacture of Oncaspar has varied through the development of the product and thus differed between the clinical trials conducted (the majority of proprietary clinical trials used the enzyme from Supplier M except study ASP-304 which used the enzyme from Supplier K) and from the native E coli L-asparaginase expected to be used in the commercial product (enzyme from Supplier L). Analytical comparability exercises showed that the resulting products were comparable (see quality aspects). In addition, a PK comparison of Supplier L and Supplier M enzymes established the relevance of the Supplier M data (see data presented under pharmacology aspects). The applicant is recommended to submit the final results of the PK/PD analysis to further assess the PK comparability between the Supplier L and Supplier M products (REC).

Oncaspar has been administered in dose-response studies with different doses (range 500 IU/m^2 – 8.000 IU/m^2), schedules (every week / every two weeks) and routes of administration (IM or IV). Most patients were eventually treated at the dose of 2.000 – 2.500 IU/m^2 every other week, consistent with the dose proposed in the SmPC. The 2500 U/m^2 body surface area every 14 days for patients with a body surface area ≥0.6 m^2 and who are ≤21 years of age can be considered well justified, taking into account the comprehensive data submitted.

For children with BSA <0.6m^2, it is acknowledged that the optimum dosage has not been rigorously investigated in clinical trials. However, the recommended posology of 82.5 IU/kg body weight for children with a body surface area < 0.6 m^2 every 14 days is justified based on data available experience (see SmPC section 4.2).

In patients under 55 years old, the optimal posology of Oncaspar appears to be 2000 IU/m^2 with a 2 – weekly dosing schedule. Data in elderly patients are scarce (see SmPC section 4.2).

Efficacy data and additional analyses

The applicant presented data to support the use of Oncaspar in the treatment of patients with acute lymphoblastic leukaemia (ALL) which includes both first line and second line treatment. The first line treatment concerns newly diagnosed patients never treated for their disease (patients non hypersensitive to native asparaginase) and the second line treatment concerns patients with one relapse/treatment failure. In the context of a second line treatment, Oncaspar has been assessed

when it is used in first intention, i.e. when native asparaginase could be used and also when it is used in second intention, i.e. when native asparaginase cannot be used due to hypersensitivity.

Four clinical trials (CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01) were initially provided in support of the indication in first line non-hypersensitive population. The main study supporting the use of Oncaspar in first line, non-hypersensitive patients is study CCG-1962. The applicant also submitted the CSR of study AALL07P4 as well as the statistical report of study DFCI 05-001 in support of this indication. Overall, 720 patients were treated with Oncaspar in first-line across these three studies.

Study CCG-1962 compared a single injection of Oncaspar (2.500 IU/m^2) during induction and Delayed Intensifications vs. 9 injections of native E-coli L-asparaginase (6.000 IU/m^2) during induction and 6 during each Delayed Intensification. From an efficacy point of view, this study was not specifically powered to detect event free survival (EFS) and overall survival (OS) differences between treatment groups. However, the results were considered clinically relevant. The overall 3 - year EFS was 83% in Oncaspar arm and 79% in native asparaginase arm. The 7-year EFS were 75% in Oncaspar versus 66% in native asparaginase arm.

With regards to immunogenicity data collected in study CCG-1962, as tests used to detect antibodies were different from an arm to another, no conclusion can be drawn on the comparability between the immunogenicity of pegaspargase versus native asparaginase. Nevertheless, immunogenicity data were obtained in several studies through the development program indicating reduced immunogenicity for pegaspargase.

With regards to study DFCI-05-001, only patients with an optimal response with an Oncaspar containing induction regimen could be randomised to receive either Oncaspar (2.500 UI/m^2 every two weeks) or weekly doses of native E. coli L-asparaginase (25.000 IU/m^2) in all the subsequent treatment phases. However, from a PD point of view, data from this study are reassuring: in the 87% of patients asparaginase activity measured at day 25 of induction (i.e. approximately 18 days after a single dose of Oncaspar) was not below the therapeutic level (> 0.10 IU/ml). Moreover, in all subsequent treatment phases, asparaginase activity was constantly significantly higher in patients treated with Oncaspar compared with native E. coli asparaginase. From an efficacy point of view, no significant differences between treatment groups in study DFCI-05-001 with respect to 5-year EFS and OS rates could be observed. However, it should be pointed out that, since all patients were treated with Oncaspar during induction (i.e. the treatment phase in which the bulk of cytoreduction is achieved), any possible difference in efficacy between the two asparaginases might have been lessened. The 5-year OS rates in both treatment arms in this study were clinically relevant (96% with Oncaspar and 94% with native E. coli asparaginase).

Results from study AALL07P4 supported the efficacy of Oncaspar when used in first-line (3-year EFS 85%, 3-year OS 92.4%).

The Applicant also conducted an additional systematic review of the literature to provide additional data to support the non-inferiority of Oncaspar compared to native E. coli asparaginase in first-line (data not shown). Overall, 646 publications were identified, and only 40 publications were considered for analysis. Due to the lack of direct and indirect comparison data, however, no meta-analysis exercise could eventually be performed. The Applicant provided separate pooled estimates of outcomes and events. Overall, results from all pooled analyses did not show any significant reduction in the efficacy outcomes observed when Oncaspar is used upfront.

Overall, the administration advantages of Oncaspar compared with native E. coli asparaginase (including reduced immunogenicity) are acknowledged. The advantages in terms of posology with Oncaspar (i.e. less frequent administrations) were supported by an exploratory HR-QoL analysis performed in study DFCI-05-001. Reduced procedural anxiety scores in parents-proxy as well as in patients were observed with Oncaspar compared with native *E. coli* L-asparaginase.

The efficacy of Oncaspar was also assessed in patients with ALL with one relapse/treatment failure (second line indication). Most of the relevant data submitted in this application concerning the benefit of Oncaspar in second line indication comes from a single comparative study ASP-304. Additional supportive studies provided relevant data in patients previously treated and hypersensitive to native asparaginase. Five open-label studies (ASP-001, ASP-001C/003C, ASP-201A, ASP-302, ASP-400) evaluated Oncaspar in relapse/refractory haematological diseases.

In these six studies a total of 94 patients with ALL diagnosis with a history of prior clinical allergic reaction to native E. coli L-asparaginase were exposed to Oncaspar. One patient received Oncaspar doses of 250 and 500 Units/m^2 intravenously. The remaining patients were treated with 2000 or 2500 U/m^2 administered intramuscularly or intravenously. Patients received Oncaspar as a single agent or in combination with multi-agent chemotherapy. Overall, from five studies analysed (ASP-001, ASP-304, ASP-201A, ASP-302, ASP-400) based on 65 ALL patients exposed to Oncaspar using the highest therapeutic response during the entire study, complete remission were observed in 30 patients (46%), partial remission in 7 patients (11%) and haematological improvement in 1 patient (2%). In study ASP-001C/003C, with 29 hypersensitive ALL patients exposed to Oncaspar, 11 patients were evaluated for response during induction. Of these, 3 patients achieved complete remission (27%), 1 patient had partial remission (9%), 1 patient had haematologic improvement (9%) and 2 patients had therapeutic efficacy (18%). Therapeutic efficacy was defined as a clinical improvement which did not meet the criteria for other beneficial outcomes. During the maintenance phase, 19 patients were evaluated, with 17 patients achieving complete remission (89%), and 1 patient with therapeutic efficacy, (5%) (see SmPC section 5.1).

In this population of patients hypersensitive to native asparaginase, no direct randomised comparative study versus native asparaginase is warranted and the provided data are considered sufficient. Results of study ASP-304 show that in ALL patients, in second relapse, Oncaspar, as part of the induction regimen permits to obtain a complete remission rate of 41%. These results taken together with the impossibility to reintroduce the native E. coli asparaginase in hypersensitive patients are sufficient to establish the efficacy of Oncaspar in second line in patients hypersensitive to native asparaginase.

Patients who are not hypersensitive to asparaginase still have the option to receive native asparaginase in second line treatment. Results from the comparative randomised study ASP-304 versus native E. coli asparaginase showed a negative trend concerning Oncaspar in terms of complete remission rates. However, the observed CR difference lacks statistical significance, possibly due to the fact that inclusions were stopped before reaching the planned sample size. Moreover, results from the additional single arm studies are of poor reliability and are difficult to interpret, especially since they show contradictory trends. Overall, even though the absence of evidence of inferiority does not imply that non-inferiority has been proved, it should also be taken into account that, after the observation by Tong at al. (Blood 2014) that the use of native E coli asparaginase in first-line induction led to high hypersensitivity rates to PEGasparaginase in the subsequent intensification phase (the so called silent inactivation), in the clinical practice the use of native E. coli L-asparaginase in first-line has seen a significant reduction. In patients treated with PEGasparaginase in first line there is no clinical rationale to switch to native asparaginase in second line, due to the potential occurrence of hypersensitivity reactions. Therefore the issue of the lack of compelling comparative data between Oncaspar and native asparaginase in the second line is considered to not significantly impact on the efficacy assessment of Oncaspar.

Based on the totality of the data, the use of Oncaspar in patients non-hypersensitive to native asparaginase in first line and in second line is considered adequate. However, the CHMP considered that further data were needed to further characterise the efficacy of Oncaspar in this subpopulation of patients who are non-hypersensitive to native asparaginase. Therefore, the Applicant will submit results from a post- authorisation efficacy study CAALL-F01 to further investigate the efficacy,

safety and PK/PD/immunogenicity of Oncaspar when used in first-line in paediatric setting. The final clinical study report is expected by 31 December 2025 (Annex II condition). Interim report after 3 year of inclusion will be provided by 31 December 2019 as detailed in the RMP.

Most of the trials have been performed in children, adolescents and young adults. However, it is considered shown that asparaginase has a benefit in ALL adult patients based on available literature data (see supportive studies). Therefore, the CHMP does not recommend a restriction of the use of Oncaspar according to age.

Furthermore, additional efficacy data will be provided in this subpopulation (adult patients) from a clinical trial investigating safety and efficacy when Oncaspar is used in the first-line treatment along with multi-agent chemotherapy in adults with ALL (Annex II condition). The final study report of this a post- authorisation efficacy study is to be provided by 31 December 2018. This trial will also provide further supportive data to characterise the efficacy of Oncaspar in patients non-hypersensitive to asparaginase.

No data are available in high risk ALL Ph+ patients and, as a consequence, a warning has been included in the SmPC of Oncaspar (see SmPC section 4.4).

2.5.4. Conclusions on the clinical efficacy

Overall, the provided data support the efficacy of Oncaspar in ALL patients who are hypersensitive to native asparaginase. In addition, the many studies supporting the efficacy of the product, and the clinical experience that has been gained on this product in post-marketing, efficacy can be considered established in patients non-hypersensitive to native asparaginase both in first line and second treatment.

The CHMP considers the following measures necessary to address issues related to efficacy:

The CHMP consider that additional data are necessary to confirm the benefit of Oncaspar in the subgroup of ALL patients who are non-hypersensitive to native asparaginase and in the subgroup of adult patients with ALL respectively:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in patients with newly diagnosed acute lymphoblastic leukaemia, the MAH should submit the results of Study CAALL-F01, a prospective multicentre cohort study evaluating Oncaspar used in the first-line treatment of children and adolescents with ALL along with multi-agent chemotherapy. The clinical study report should be submitted by:	December 2025
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in adult patients with ALL, the MAH should submit the results of a multicenter, open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar in adults (aged 18-60) with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukemia. The clinical study report should be submitted by:	December 2018

2.6. Clinical safety

No integrated safety database has been submitted for pegasparagase and multiple data sources contribute to definition of safety profile. In particular, the safety data were derived from:

- The original package submitted in the second-line MAA filed in 1994 in Germany (studies ASP-001, ASP-001C/ASP-003, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400). These data are mostly on patients hypersensitive to native E.coli ASNase before exposure to PEG-ASNase;

- Studies performed to support the first-line indication in US (studies CCG-1961, CCG-1962, DFCI-87-001 and DFCI-91-01). Study CCG-1991 is also included in this group, although PEG-ASNase is part of the background therapy. The majority of patients included in this study were naive to asparaginase and therefore can be considered not-hypersensitive;

- Post-marketing use, including data collected by the original MAH of pegasparagase in EU (PSUR version 4.0), data from commercialisation in US and those from academic, studies in which PEG-ASNase is part of a combination regimen (i.e, AIEOP-BFM, ALL-2009, ALL-MB 2008, CO-ALL-08-09, DCOG ALL-11, GMALL 07/2003, HOVON 100 ALL/EORTC 06083, IntReALL SR 2010, MC-PEGASP.1/Adults, NOPHO ALL2008, UK ALL 2011, UK ALL14).

The majority of the clinical trials enrolled ALL paediatric patients, but other haematological malignancies (e.g, Non-Hodgkin Lymphoma) were also represented. In addition, adult patients with solid tumours and NHL were included in study ASP-102 and ASP-203.

Preliminary safety data of study AALL07P4, that is part of the development program for a new pegylated ASNase and in which PEG-ASNase was used as a control treatment, were also submitted.

Patient exposure

Patient exposure from clinical trial experience was 5,304 patients and in post-marketing experience was 91,833 patients. The paediatric population represented the main target population for pegasparagase (more than 95%). The IM route of administration was mainly used during clinical trials (more than 95%).

The method used to calculate patient exposure was as follows: The average dosage per patient per application is established as 3,750 IU (content of a single vial of pegasparagase) and the average duration of treatment as four applications per patient. Therefore, the number of patients exposed to pegasparagase was calculated as an average dose of 15,000 IU per patient.

Table 62: Patient exposure in controlled studies and in post-marketing phase

	Patients exposed	Patients exposed to the proposed dose range
Active -controlled		
Open studies[a]	5,304	5,103
By age[a]		
Adults	85	
Paediatrics patients	5,178	
Unspecified	41	
By route of administration[a]		
Intramuscular	5,127	
Intravenous	135	
Both	42	
Post marketing	91,833	
Germany	19,007	
U.S.A and Canada	55,274	
Other countries with EU product	15,714	
Other countries with US product	1,838	
Compassionate use		

[a] *Includes study subjects of studies ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400, ASP-102, ASP-203, CCG-1961, CCG-1962, DFCI-87-001, DFCI-91-01, CCG-1991 and AALL07P.*

Details on patients exposed to pegasparagase in relevant clinical studies, starting from the original MA in 1994, are reported in the following Table:

Table 63: Summary of patient exposure in clinical trials

Data sources	Hypersensitive patients	Non-Hypersensitive patients	PEG-ASNase dose & schedule
Clinical trials			
Second line original data package (1994)*	78	172	500,1000,2000,2500,4000,8000 IU/m^2 IV 2000, 2500 IU/m^2 IM
Study CCG-1961	142	138	2500 IU/m^2 IM
Study CCG-1962	0	57	2500 IU/m^2 IM
Study DFCI-87-001	0	84	2500 IU/m^2 IM
Study DFCI-91-01	0	377	2500 IU/m^2 IM
Study CCG-1991●	0	2957	2500 IU/m^2 IM
Study AALL07P4◇	0	51	2500 IU/m^2 IM

* including studies ASP-001, ASP-001C, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400

°every 2 weeks during induction and every 2 to 16 weeks during continuation therapy

● enrolled newly diagnosed and previously untreated patients with ALL between ages 1 through 9 years

◇ pilot study of intravenous EZN-2285 (SC-PEG *E. coli* L-asparaginase) or intravenous pegasparagase® in the treatment of newly diagnosed patients with high-risk ALL

Overall data on exposure are available for second line studies.

PEG-ASNase was administered intravenously in 92 patients (18 hypersensitive and 74 non-hypersensitive), while the intramuscular route was used in 158 patients (60 hypersensitive and 98 non- hypersensitive).

Table 64: Summary of PEG-ASNase doses and routes of administration

HYPERSENSITIVE to ASPARAGINASE	ROUTE	NO. OF PATIENTS	DOSES	
			TOTAL	RANGE
Yes	i.v.	18	58	1 - 10
Yes	i.m.	60	326	1 - 29
No	i.v.	74	218	1 - 22
No	i.m.	98	432	1 - 37

Overall, 384 doses were administered to the 78 hypersensitive patients and 650 to the non-hypersensitive patients.

Long term safety data (defined as any patient who received >2 doses of PEG-ASNase which is equivalent to at least 4 weeks of therapy with native *E coli* L-asparaginase) were available for 121 patients.

The range of treatment days and the number doses of PEG-ASNase for the hypersensitive and non-hypersensitive patients are presented below:

Table 65: Summary of days on study for patients on PEG-ASNase therapy

DAYS ON STUDY	HYPERSENSITIVE PATIENTS		NON-HYPERSENSITIVE PATIENTS	
	N	%	N	%
1-14	5	(6.4)	20	(11.6)
15 - 30	26	(33.3)	42	(24.4)
31 - 60	17	(21.8)	47	(27.3)
61 - 90	7	(9.0)	32	(18.6)
91 - 180	10	(12.8)	18	(10.5)
181 - 365	9	(11.5)	9	(5.2)
> 365	4	(5.1)	4	(2.3)

Source: : Legacy Summaries of Efficacy and Safety page 80

The median number of days on study was 43 (range 1 to 640 days) for all patients, 43 days (range 1 to 559 days) for the hypersensitive patients and 43 days (range 1 to 640 days) for the non-hypersensitive patients.

Table 66: Summary of PEG-ASNase doses for patients on therapy

DOSES OF ONCASPAR	HYPERSENSITIVE PATIENTS		NON-HYPERSENSITIVE PATIENTS	
	N	%	N	%
1	8	(10.3)	35	(20.4)
2	35	(44.9)	51	(29.7)
3	7	(9.0)	38	(22.1)
4 - 6	8	(10.3)	28	(16.3)
7 - 10	10	(12.8)	10	(5.8)
11-20	7	(9.0)	7	(4.1)
> 20	3	(3.9)	3	(1.7)

Source: : Legacy Summaries of Efficacy and Safety page 80

The median number of doses administered was 2 (range 1 to 37 doses) for all patients, 2 (range 1 to 29 doses) for the hypersensitive patients, and 3 (range 1 to 37 doses) for the non-hypersensitive patients.

Regarding studies investigating first line use, the extent of exposure to study medication has been retrieved for study CCG-1962 for whom a clinical study report has been provided. Details are reported in the following table:

Table 67: Extent of exposure to PEG-ASNase and native ASNase in CCG-1962

	PEG-ASNase			Native ASNase		
Treatment phase	Induction	DI #1	DI #2	Induction	DI #1	DI #2
Assessable patients	59	54	48	59	53	53
Dose of drug	2500 IU/m^2	2500 IU/m^2	2500 IU/m^2	6000 IU/m^2	6000 IU/m^2	6000 IU/m^2
Days of treatment	Day 3	Day 3	Day 3	Days 3, 5, 8, 10, 12, 15, 17, 19, 22	Days 3, 5, 8, 10, 12, 15	Days 3, 5, 8, 10, 12, 15

Table 68: Compliance by treatment (Study CCG-1962)

% Compliance	Native *E. coli* ASP N=59 n (%)	PEG-ASP (Oncaspar) N=59 n (%)
19.0	1 (1.7)	0 (0.0)
28.6	3 (5.1)	0 (0.0)
33.3	1 (1.7)	3 (5.1)
42.9	1 (1.7)	0 (0.0)
52.4	1 (1.7)	0 (0.0)
66.7	0 (0.0)	8 (13.6)
71.4	1 (1.7)	0 (0.0)
100.0	51 (86.4)	48 (81.4)

Abbreviations: ASP=asparaginase, PEG-ASP=pegylated asparaginase

%Compliance = 100* total number of doses taken /planned number of doses; where the planned number of doses was 21 for native asparaginase, and 3 for oncaspar. If over 100% then considered as 100%.

In study DFCI-05-001, the target number of doses administered for each treatment arm (30 for native E. coli ASP administered weekly and 15 for PEG-ASP [pegasparagase] administered every 2 weeks) in the first line treatment of ALL is shown in the Table below.

Table 69: Target number of doses of asparaginase in DFCI-05-001 and switch to another asparaginase by treatment group (Oncaspar versus native E.Coli ASP)

N	PEG-ASP (Oncaspar)	Native *E. coli* ASP	p-value[a]
No. of Patients with 100% of Target Doses Administered:[b]	N=232	N=231	0.015
Yes	191 (82)	170 (74)	
No	41 (18)	61 (26)	
No. of Patients with ≥87% of Target Doses Administered:[c]			0.11
Yes	205 (88)	192 (83)	
No	27 (12)	39 (17)	
No. Patients who Switched Preparations:	29 (13)	38 (16)	0.24
Switched to Erwinia ASP	26 (11)	6 (3)	
Switched to PEG-ASP (Oncaspar)	3 (1)	32 (14)	

Abbreviations: ASP=asparaginase, PEG-ASP=pegylated asparaginase

[a] Comparison made between randomisation arms

[b] At least 30 doses if randomised to native *E. coli* ASP or at least 15 if randomised to PEG-ASP (Oncaspar)

[c] At least 26 of 30 doses administered if randomised to native *E. coli* ASP or at least 13 of 15 if randomised to PEG-ASP (Oncaspar)

Based on data from Periodic Safety Update Reports and sales data, it is estimated that PEG-ASNase has been used to treat more than 42.000 in European countries and further 57.000 patients in other regions including North America.

Therefore, the overall estimated number of patients treated with PEG-ASNase through 20 years is over 100.000, combining clinical trials and commercial use.

Adverse events

The applicant's safety databases include data from all available sources (i.e. clinical trials, spontaneous reporting and published literature). The total number of patients covered by the safety database is estimated at 101,200.

The table is the result of combining sub-tables corresponding to reports of adverse events following exposure to Oncaspar Supplier M (n=50,646), Oncaspar Supplier K (n=31,477) and Oncaspar Supplier L (n=19,077).

Table 70: Adverse reactions reported with Oncaspar therapy

MedDRA Standard System Organ Class	Adverse Reaction
Infections and infestations	Common: Infections, Sepsis
Blood and lymphatic system disorders	Common: Febrile neutropenia, Anaemia, Thrombosis
Immune system disorders	Very common: Hypersensitivity, Urticaria, Rash, Anaphylactic reactions
Endocrine disorders	Very Common: Hyperglycaemia
Metabolism and nutrition disorders	Common: Hypertriglyceridaemia, Hyperlipidaemia
Nervous system disorders	Common: Convulsion, Peripheral Motor Neuropathy, Syncope

Vascular disorders	Common: Thrombosis
Respiratory, thoracic and mediastinal disorders	Common: Hypoxia
Gastrointestinal disorders	Very common: Pancreatitis, , Diarrhoea, Abdominal pain Common: Vomiting, stomatitis
Musculoskeletal and connective tissue disorders	Common: Pain in extremities
Investigations	Common: Amylase increased, Alanine aminotransferase increase, Blood bilirubin increase, Neutrophil count decreased, Platelet count decreased, Activated partial thromboplastin time prolonged

Second line treatment

Results from the following eight clinical studies were provided: ASP-001, ASP-001C, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400. Two-hundred-and-fifty (250) patients were assessable for safety in all second-line studies.

IM administration: A total of 57 (44%) of the 126 patients reported CTC grade 3 or 4 non-allergic reactions, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 31 patients. Changes in liver function tests were noted in 41 patients. A total of 3 patients reported other CTC grade 3 or 4 non-allergic, known L-asparaginase toxicities (other than chemical coagulopathies and chemical hepatotoxicities), which were possibly, probably or definitely related to pegasparagase. The probability of not developing a non-allergic CTC grade 3 or 4 reaction by the third dose for the 60 hypersensitive and 66 non-hypersensitive patients was 58% and 13%, respectively.

IV administration: A total of 47 of the 92 patients reported CTC grade 3 or 4 non-allergic toxicities, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 11 patients. Changes in liver function tests (CTC grades 3 and 4) were noted in 35 patients (38%). The probability of not developing a non-allergic CTC grade 3 or 4 reaction by the third dose for the 18 hypersensitive and 74 non-hypersensitive patients was 49% and 48%, respectively.

Safety regardless of route of administration: A total of 104 (48%) of the 218 patients (26 hypersensitive and 78 non-hypersensitive) who received pegasparagase reported CTC grade 3 or 4 non-allergic toxicities, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 42 patients. Changes in liver function tests were noted in 76 patients. Finally, six patients (3%) experienced CTC grade 3 increases in BUN and 2 (1%) had neurological dysfunctions.

Study ASP-304

The most frequently occurring toxicities (regardless of CTC grade), were hepatotoxicity and coagulopathy, the majority of which were laboratory abnormalities without clinical manifestations.

An examination of the expended toxicologic data demonstrated that there was a high incidence of hypoproteinemia observed during induction therapy for this study. Although 16 (40%) of 40 pegasparagase direct assigned patients, 9 (47%) of 19 randomized pegasparagase patients and 11 (65%) of 17 Elspar patients experienced hypoproteinemia during therapy, there was no significant difference in incidence between the two randomized treatment groups (p=0.335). There were no incidences of bleeding disorders or increased creatinine in any of the treatment groups. The overall

incidence of known L-asparaginase toxicities which occurred during induction therapy similar for randomized pegasparagase and Elspar patients, with coagulopathy being the only toxicity demonstrating a significant difference (p=0.003) in favour of the pegasparagase patients. Of all of the coagulation abnormalities reported (regardless of CTC grade), decreased fibrinogen demonstrated a significant difference between the two randomized patient populations during therapy (p=0.006).

Fifteen (79%) of 19 patients randomized to pegasparagase had a total of 26 drug related adverse experiences with an average duration of 10.3 days. The most common (greater than ten percent) ONCASPAR related adverse experiences were hypoproteinemia (47%), increased SGPT (32%) and hyperbilirubinemia (16%), decreased fibrinogen (11%), and increased partial thromboplastin time (11%). There was no difference in the incidence of adverse experiences between the "regardless of relationship to study drug" and ''related to study drug" tables.

Thirty-three (83%) of 40 patients directly assigned to pegasparagase had a total of 75 drug related adverse experiences with an average duration of 13.5 days. The most common (greater than five percent) oncaspar related adverse experiences were increased SGPT (45%), hypoproteinemia (40%), decreased fibrinogen (30%), increased partial thromboplastin time (15%), hyperbilirubinemia (15%), and fever (8%) and allergic reactions. The only adverse experiences that demonstrated an increased frequency of occurrence from the "related to study drug" to "regardless of relationship to study drug" tables were fever (from 8% to 10%) and urticaria (from 3% to 8%).

The most frequent adverse events observed in second-line use studies, (except immunological events) were abnormal liver test (hyperbilirubinemia, increased SGPT/SGOT, decreased albumin, hypoproteinemia and fatty liver), pancreatitis (hyperamylaseamia), coagulopathy (decreased fibrinogen, increased partial thromboplastin time), central nervous system thrombosis. Other adverse events (less frequent) were gastro-intestinal disorder (nausea, vomiting, diarrhoea), chills, fever, neurologic disorder (peripheral neuritis, pain in extremity).

First line treatment

Results taken from the following four clinical studies were provided: CCG-1962, CCG-1991, DFCI-87-001 and DFCI-91-01.

Study CCG-1962: Infections were the most toxic events. As regards CNS thrombosis, among the occurrence in the PEG-ASNase treatment, one occurred during induction and the second Day 22 of delayed intensification #1. As regards pancreatitis, one event occurred in each arm during induction. There were two additional occurrences of pancreatitis in the PEG-ASNase group and during delayed intensification #2. For some other adverse events (allergic events, pancreatitis, abdominal pain), more cases have been reported with pegasparagase than with Elspar. As an example, there were 3 cases of pancreatitis with pegasparagase versus 1 case for native asparaginase whatever the treatment phase. There was however no quantitative measurable difference in the safety profile between pegasparagase and Elspar.

Study CCG-1991: The main reported adverse events were immune system disorders, CNS disorders, blood and lymphatic systems and gastrointestinal disorders.

Serious adverse event / deaths / other significant events

Serious adverse event

From the initiation of the pegasparagase program on March 31, 1984 through to the cut-off date for the analysis of May 31, 1990, 28 serious adverse drug experiences were reported to the United States FDA. Fifteen of these reports occurred with the intravenous administration of pegasparagase during study ASP-001. Eight of these 15 reports from ASP-001 were on-study deaths due to

progressive disease. These deaths were expected because at study entry the patients had life expectancies of approximately six weeks. In addition, 4 other disease-related deaths were reported for studies ASP-201A, ASP-203 and ASP-302. Thirteen other patients reported serious adverse drug experiences which included anaphylaxis, bronchospasm, convulsions, CNS haemorrhage, disorientation, pancreatitis, thrombosis, paresthesia, a systemic hypersensitivity reaction and haemolytic anaemia. None of the 10 E coli L-asparaginase patients, to the applicant's knowledge, experienced any serious adverse experiences.

Study CCG-1962: A total of five patients (4.2%) had non-fatal SAEs (3 Peg-asp patients and 2 native asp patients). The following SAEs were reported: Grade 3 or 4 coagulopathy, Grade 3or 4 pancreatitis, and Grade 4 neurologic dysfunction; foot pain; Grade 4 CNS toxicity; and Grade 3 or 4 coagulopathy and Grade 4 neurologic dysfunction.

Deaths

There were 102 deaths among the 250 patients treated with pegasparagase in the clinical trials investigating second-line use of pegasparagase. Of these deaths, 22 occurred on-study and 80 off-study. The off-study deaths occurred between 2 and 453 days after study termination. All deaths, were considered to be disease-related. There were 5 deaths among the 10 patients treated with native *E coli*-derived L-asparaginase in the clinical trials investigating second-line use of pegasparagase. All these deaths were considered to be disease-related and all occurred off-study between 62 and 307 days after study termination.

Clinical study reports and publications for studies in which pegasparagase was used in first-line therapy (CCG-1961, CCG, 1962, CCG-1991, DFCI-87-001 and DFCI-91-01) identify 39 deaths of which 32 occurred in patients receiving pegasparagase, 6 in patients treated with native *E coli*-derived L-asparaginase and 1 in a patient treated with *Erwinia*-derived enzyme. None of these deaths was specifically attributed to asparaginase therapy.

Immunological events

Data on immunological events are based on studies that supported the Marketing Authorization in 1994. The main allergic AEs are urticarial, rash, dyspnea, bronchospasm, tachycardia, hypotension and anaphylactic shock. One case of toxic epidermal necrolysis (Lyell's syndrome) has been described.

The analysis of patients included in the 1994 MAA for whom both the following were as follows:

- Nature and grade of hypersensitivity reaction to native asparaginase.
- Nature and grade of hypersensitivity reaction to pegasparagase

8 of the 13 patients with previous Grade 4 hypersensitivity reactions did not experience any hypersensitivity after pegasparagase administration (61.5%). Two patients had a Grade 1 reaction (15.4%), 2 had a Grade 2 reaction (15.4%) and 1 patient had a Grade 4 reaction (7.7%). Only 1 patient (7.7%) with previous Grade 4 hypersensitivity to native enzyme had a hypersensitivity reaction >Grade 2 when given pegasparagase. A similar analysis has been conducted for patients who suffered a Grade 3 reaction to native asparaginase prior to treatment with pegasparagase. 17 of the 21 patients with previous Grade 3 hypersensitivity reactions did not experience any hypersensitivity after pegasparagase administration (81%). Two patients had a Grade 1 reaction (10%) and 2 had a Grade 3 reaction (10%). There were no Grade 2 or Grade 4 reactions. Only 2 patients (10%) with previous Grade 3 hypersensitivity to native enzyme had a hypersensitivity reaction >Grade 2 when given pegasparagase.

Study CCG-1962: There were two hypersensitivity reactions in the pegasparagase treatment group (3.4%); one case of Grade 1 allergy and one case of Grade 3 hives. No cases of hypersensitivity to native asparaginase were reported.

Study CCG-1991: In accordance with the study protocol, Grade 1 & 2 allergic reactions were not recorded.

There were 9 reports of Grade 3 hypersensitivity and 5 reports of Grade 4 hypersensitivity (14 reports in all; 0.5%). The exact nature of the hypersensitivity reactions was not reported.

Study AALL07P4: There were 20 hypersensitivity reactions recorded in 15 patients. The main allergic AEs are urticarial, rash, dyspnea, bronchospasm, tachycardia, hypotension and anaphylactic shock. One case of toxic epidermal necrolysis (Lyell's syndrome) has been described. The probability of Grade 3/4 toxicity in hypersensitive patients was higher with PEG-ASNase administered intravenously than intramuscular. Data supporting the role of neutralising antibodies in leading the different risk based on route of administration were not available.

Post-marketing

Post-marketing ADRs of hypersensitivity reports received during 1984 to 2014 via safety reports that include US, Canada, and EU were analysed. Postmarketing safety data were retrieved from the Applicant's Drug Safety Database and the hypersensitivity reactions reported remains approximately 13.7% of all reported postmarketing adverse drug reactions. Overall, allergic reactions/hypersensitivity in the 3 clinical studies with CSRs using PEG-ASP in first line ALL patients did not reach the 54%, as reported for CCG-1961 (CCG-1962, 5%; DFCI-05-001, 12%; AALL07P4, 9.8% hypersensitivity and 19.6% anaphylactic reaction). In the publication for study CCG-1962, Seibel et al (2008) reported that 54% of patients treated on increased intensity post-induction intensification arms experienced an allergic reaction to PEG-ASNase. However, there is no indication of the seriousness or severity of these allergic reactions in the publication or whether these events occurred in the longer duration or standard duration PII phases. No further information on hypersensitivity or allergic reactions were reported in available publications.

Laboratory findings

The following table presents ADRs concerning laboratory findings from the safety database.

Table 71: Adverse reactions concerning laboratory data contained in pegasparagase safety databases

SOC	Adverse reaction	Age range (years)							Total
		1 to < 2	2 to ≤ 12	>12 to ≤18	>18 to 40	40 to <65	≥65	Unknown	
Investigations	Blood Fibrinogen decreased		1				1	1	3
	Liver Function Test Abnormal		3		6	7	1	6	23
	Renal Function Test Abnormal						1		1
	Blood Bilirubin Increased		3	3	7	33	2	4	52
	Blood Triglycerides Increased		5	3	5	1		1	15
	Hepatic Enzyme Increased			1	2	4		2	9
	Alanine Aminotransferase Increased		1	2	7	12			22
	Aspartate Aminotransferase Increased		1	2	3	5		1	12
	GGT Increased				2	7			9
	Anti-Thrombin III Decreased		1		1				2
	Weight Decreased/ Weight Loss				1	1			2
	Blood Lactic Acid Increased			2	1				3
	Platelet Count Abnormal		1		1				2
	Blood Fibrinogen Decreased			1		1	1		3
	Clotting Time Prolonged						1		1
	T Wave Inversion					1			1
	Blood Count Abnormal					1			1
	Albumin Abnormal			1	1			1	3
	Creatinine Increased					1			1
	Blood Creatine							1	1
	Neutrophil Count Decreased					2			2
	Serum Amylase Increased			2		1			3
	Alkaline Phosphatase Increased				7	22		1	30
	Abnormal Coagulation Profile					1			1
	Lipase increased			1					1
	Hemoglobin decreased		2	1					3
	Prothrombin time prolonged		1	2				1	4

SOC	Adverse reaction	Age range (years)							Total
		1 to < 2	2 to ≤ 12	>12 to ≤18	>18 to 40	40 to <65	≥65	Unknown	
	Laboratory test abnormal		1	1					2
	Partial thromboplastin time prolonged			1				1	2
Blood and lymphatic system disorders	Anaemia		3		1	1	1		6
	Coagulopathy	1	1	3	2	1		1	9
	Febrile Neutropenia	1	3		13	7	1	2	27
	Disseminated Intravascular Coagulation		3	2		1		1	7
	Pancytopenia	1	2	2			1		6
	Hemolysis				1				1
	Neutropenia	1	8	1	2			3	15
	Abnormal Clotting Factor				1				1
	Haemophagocytic lymphohistiocytosis			1					1
	Granulocytopenia			2					2
	Thrombocytopenia		2	1					3
	Autoimmune Haemolytic Anaemia					1			1
Metabolism and nutrition disorders	Hypercalcaemia						1		1
	Hyperglycaemia		3	4	2	3		2	14
	Hyperkalaemia		1						1
	Hypocalcaemia		1	5					6
	Hypoglycaemia		5	1					6
	Hypophosphataemia				1				1
	Hyponatraemia		1	4	2	1			8
	Inappropriate Antidiuretic Hormone Secretion					1			1
	Cholesterol High/ Hypercholesterolemia		1	3	2				6
	Hyperlipidaemia		6	4				2	12
	Hyperammonemia		3	3	1			1	8
	Hypokalaemia				1				1
	Acidosis		2	1				1	4
	Hypomagnesemia			1					1

A total of 55 terms were reported. Of these, 34 terms (62%) were reported fewer than 5 times and a further 11 terms (20%) were reported 5-9 times.

Three terms were reported 10-14 times (aspartate aminotransferase (ASAT) increased, hyperglycaemia and hyperlipidaemia). Regarding age distribution:

- 8/12 cases of ASAT increase were in adults and 5 of these were in patients aged ≥40 years.
- 10/12 cases of hyperlipidaemia were in children, while the remaining 2 cases were in patients of unknown age.
- Hyperglycaemia appeared to be evenly distributed across the age range. Two terms were reported 15-19 times (blood triglycerides increased and neutropenia).
- For neutropenia, 8/15 cases (53%) occurred in patients aged 2 to <12 years.

Five terms were reported >20 times:

- There were 22 cases of increased alanine aminotransferase (ALAT). 19/22 (86%) occurred in adults and 12/22 (55%) were in patients aged ≥40 years.
- There were 23 reports of abnormal liver function. A high proportion of these reports did not include the age of the patient (6/23; 26%). Nevertheless, an increasing risk with advancing age appears likely with 13/23 reports (57%) occurring in adults and 7/23 (30%) in those aged ≥40 years.
- There were 27 reports of febrile neutropenia, increasing risk with age as 20/27 reports (74%) concerned adults. Most cases (13/27; 48%) were in young adults aged 18-40 years.
- There were 30 reports of increased alkaline phosphatase (AP) of which 29/30 (97%) were in adults and the age of the other case was unknown. The majority of reports (22/30; 73%) were in patients aged ≥40 years.

- There were 52 reports of increased blood bilirubin. Here again, older patients were more at risk with 42/52 cases (81%) occurring in adults and 35/52 (67%) occurring in patients aged ≥40 years.

Regarding neutropenia, 10/12 reports for which the patient's age is known (83%) occurred in children. However, for febrile neutropenia the situation is reversed with 21/25 cases for which the patient's age is known (84%) occurring in adults.

Combining the 2 terms and disregarding reports for which the patients' ages are not known:

- There were 14 cases of neutropenia in children of which 4 were febrile (29%).
- There were 23 cases of neutropenia in adults, of which 21 were febrile (91%).

Safety in special populations

Pregnancy

A single case of pegasparagase use in a pregnant woman was reported to the applicant. The patient concerned was 28 weeks pregnant and received 2 doses of pegasparagase i.m. which was well tolerated (no coagulopathy, mild hypertriglyceridaemia). The foetus reportedly gained 260g in the 3-week interval between the first pharmacovigilance communication (believed to be pre-pegasparagase dosing) and the follow-up notification confirming that two doses of pegasparagase had been administered. Delivery was induced at 33 weeks and resulted in a female child weighing 2,113g. Foetal hypoxia was noted during delivery. Cardiac ultrasound revealed multiple muscular septal defects. In the literature, 6 cases of pregnancy (and 7 births) have been reported with an exposure to L-asparaginase during the second and third trimester of pregnancy (Okun 1979, Khurshid 1978, Karp 1983, Awidi 1983, Turchi 1988, Schlieuning 1987). However, no case has been reported with an exposure during the first trimester of pregnancy.

Concerning foetotoxic effect of ONCASPAR, leucopenia has been reported in two cases in new-borns following in utero exposure to L-asparaginase in combination with others therapies (Okun 1979, Khurshid 1978).

There is no data submitted on pegaspargase excretion into breast milk.

Age

The majority of the clinical data has been collected in patients 2-21 years old, especially in second line clinical trials which almost exclusively featured patients in this age range. Broader age representation has been accumulated in first-line ALL clinical studies, in study INTERFANT-06 (specifically for infants aged <1 year), and commercial sales.

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies on drug-drug interactions.

Discontinuation due to adverse events

Thirty-seven patients (14 patients hypersensitive and 23 non-hypersensitive) had their treatment with pegasparagase discontinued due to adverse experiences. Seventeen patients (12 hypersensitive and 5 non-hypersensitive) experienced either local or systemic hypersensitivity reactions (CTC grades 1 to 4). Ten patients (2 hypersensisitive and 8 non-hypersensisitve) experienced non-allergic toxicities (CTC grades 1 to 4) to pegasparagase and 1 non-hypersensitive patients from studies ASP-102 and ASP-103 experienced known L-asparaginase toxicities to pegasparagase. These toxicities included chemical coagulopathy and hepatoxicity, gastrointestinal disorders, disorientation, thrombosis, convulsion, nausea, weight loss, erythema simplex, myalgia and pain at the injection site.

Post marketing experience

Exposure data are presented under patient exposure.

Medac was the original MA holder for pegasparagase in the EU and remained so until the authorisation was transferred to the Sigma-Tau group 2012.

The latest available Medac PSUR (version 4.0) for pegasparagase summarised the safety data received from worldwide sources between August 2009 and July 2012. In addition to the German and Polish MAs, authorisations in Argentina, Belarus, Kazakhstan, Russia and Ukraine were included in the PSUR scope. US post-authorisation data were excluded.

Approximately 207,352,500 IU of product were sold worldwide during the monitoring period for PSUR version 4.0 which corresponded to an estimated number of 13,824 treated patients. Overall, 93 case reports were received. These included 128 listed reactions and 9 unlisted reactions (4 of which were serious). Of these, 27 were spontaneous reports received from regulatory authorities and health professionals, 55 were derived from studies and the remaining 11 cases were identified in literature.

The 4 unlisted serious reports were hyponatremia (n=2), acute cholangitis (n=1) and aemophagocytic lymphohistiocytosis (n=1).

It was concluded in the PSUR that these data did not change the risk / benefit profile of Ocaspar and no regulatory action was taken.

Data from commercialisation in the US

A preferred term analysis of 843 post-authorisation safety reports covering reaction onset dates from September 1994 to March 2012 was submitted. This covers a period during which the total exposure to pegasparagase in the territories concerned is estimated at approximately 57.000.

Table 72: Preferred terms reported ≥ 20 times in US spontaneous reporting (September 1994 to March 2012)

Preferred term	Number of reports	Percentage of all preferred terms reported (n=2,657)
Urticaria	157	5.9%
Hypersensitivity	153	5.8%
Anaphylactic reaction	99	3.7%
Rash	78	2.9%
Vomiting	71	2.7%
Dyspnoea	70	2.6%
Pancreatitis	61	2.3%
Pruritus	58	2.2%
Hyperbilirubinaemia	49	1.8%
Hyperglycaemia	48	1.8%
Lip swelling	44	1.7%
Abdominal pain	41	1.5%
Nausea	39	1.5%
Pyrexia	39	1.5%
Hypotension	35	1.3%
Cough	34	1.3%
Swelling face	32	1.2%
Erythema	26	1.0%
Total	**1,134**	**42.7%**

The data shows that there were 25 spontaneous reports. The first-listed events were hypersensitivity (n=11), hypertriglyceridemia (n=3), pancreatitis, hepatotoxicity, sepsis and depressed consciousness (n=2 each) and renal failure, infection and disease progression (n=1 each).

2.6.1. Discussion on clinical safety

The submitted safety data were taken from a limited number of well-designed or up to date studies. Additional safety data were presented based on spontaneous reporting and published literature data.

Patient exposure can be considered as substantial from both clinical trial experience (5,304 patients) and post-marketing (91,833 patients). The paediatric population represents the main target population for pegasparagase (more than 95%). IM route of administration has been mainly used during clinical trials (more than 95%).

Adverse events

The safety data were taken from the following eight clinical studies: ASP-001, ASP-001C, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400. Two-hundred-and-fifty (250) patients were assessable for safety in all second-line studies.

Overall, the most frequent adverse events observed in second-line use studies (except immunological events) are abnormal liver test (hyperbilirubinemia, increased SGPT/SGOT,

decreased albumin, hypoproteinemia and fatty liver), pancreatitis (hyperamylaseamia), coagulopathy (decreased fibrinogen, increased partial thromboplastin time), and central nervous system thrombosis. Other adverse events (less frequent) are gastro-intestinal disorder (nausea, vomiting, and diarrhoea), chills, fever, neurologic disorder (peripheral neuritis, pain in extremity).

For patients that received IM administration, a total of 57 (44%) of the 126 patients reported CTC grade 3 or 4 non-allergic reactions, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 31 patients. Changes in liver function tests were noted in 41 patients. A total of 3 patients reported other CTC grade 3 or 4 non-allergic, known L-asparaginase toxicities (other than chemical coagulopathies and chemical hepatotoxicities), which were possibly, probably or definitely related to pegasparagase. The probability of not developing a non-allergic CTC grade 3 or 4 reaction by the third dose for the 60 hypersensitive and 66 non-hypersensitive patients was 58% and 13%, respectively.

For patients that received IV administration, a total of 47 (51%) of the 92 patients reported CTC grade 3 or 4 non-allergic toxicities, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 11 patients. Changes in liver function tests (CTC grades 3 and 4) were noted in 35 patients (38%). The probability of not developing a non-allergic CTC grade 3 or 4 reaction by the third dose for the 18 hypersensitive and 74 non-hypersensitive patients was 49% and 48%, respectively.

For the safety in patients regardless of route of administration, a total of 104 (48%) of the 218 patients (26 hypersensitive and 78 non-hypersensitive) who received pegasparagase reported CTC grade 3 or 4 non-allergic toxicities, which were possibly, probably or definitely related to pegasparagase. Changes in coagulation profiles were noted in 42 patients. Changes in liver function tests were noted in 76 patients. Finally, six patients (3%) experienced CTC grade 3 increases in BUN and 2 (1%) had neurological dysfunctions.

Although a difference in the rate of patients that undergo allergic AE between the two routes of administration was observed (51% with intravenous administration versus 44% with intramuscular administration), no statistical comparison was performed between the routes of administration for non-immunological adverse events. Therefore, no firm conclusions can be drawn. Based on all available data, it is considered that Oncaspar can be given by intramuscular injection or intravenous infusion. For smaller volumes of Oncaspar, the preferred route of administration is intramuscular. Safety following IV route of administration will continue to be monitored as reflected in the RMP.

The safety data in first line treatment were taken from studies CCG-1962 and CCG-1991.

Study CCG-1962

Overall, the incidences and types of toxic events were very similar between PEG-ASNase and native E.coli ASNase arms. Infections were the most toxic events. CNS thrombosis, among the occurrence in the PEG-ASNase treatment, occurred once during induction and the second Day 22 of delayed intensification #1. Pancreatitis occurred once in each arm during induction.

Study CCG-1991

The main reported adverse events were immune system disorders, CNS disorders, blood and lymphatic systems and gastrointestinal disorders.

Blood and lymphatic system disorders

Oncaspar can cause mild to moderate myelosuppression, and all three blood cell lines can be affected. About half of all serious haemorrhages and thromboses affect cerebral vessels and can lead e.g. to stroke, seizures, headache or loss of consciousness. Myelosuppression and associated effects (including infections) has been identified as an important identified risk in the RMP.

Considering that oncaspar may possess immunosuppressive activity, it is possible that use of this it promotes infections in patients (see SmPC section 4.4).

The decrease in the number of circulating lymphoblasts is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely (see SmPC section 4.4).

Nervous system disorders

Oncaspar may cause Central Nervous System dysfunctions manifesting as convulsion, and less frequently confusional state and somnolence (mildly impaired consciousness). In rare cases, a reversible posterior leukoencephalopathy syndrome (RPLS) may occur. In very rare cases, mild tremor in the fingers has been described. Neurotoxicity has been identified as an important identified risk in the RMP. Reversible posterior leukencephalopathy syndrome (RPLS) has been inlcuded as an important potential risk.

Gastrointestinal disorders

About half of patients develop mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss.

Acute pancreatitis can occur commonly. There have been isolated reports of formation of pseudocysts (up to four months after the last treatment). Appropriate investigations (e.g. ultrasound) should therefore be performed up to four months after termination of Oncaspar therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended. Disturbances of exocrine pancreatic function can result in diarrhoea. Pancreatitis has been identified as an important identified risk in the RMP.

Haemorrhagic or necrotising pancreatitis occurs rarely. One case of pancreatitis with simultaneous acute parotitis has been described with L-asparaginase treatment. In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported. Serum amylase can rise during and also after the conclusion of Oncaspar therapy. Haemorrhage has been identified as an important identified risk in the RMP.

Blood and urine glucose levels should be monitored during treatment with Oncaspar as they may rise.

Renal and urinary disorders

Acute renal failure may develop in rare cases during treatment with L-asparaginase-containing regimens.

Skin and subcutaneous tissue disorders

Allergic reactions can manifest in the skin. One case of toxic epidermal necrolysis (Lyell's syndrome) has been described in association with L-asparaginase.

Endocrine disorders

Alterations in endocrine pancreatic function are observed commonly and are expressed mainly in the form of abnormal glucose metabolism. Both diabetic ketoacidosis and hyperosmolar hyperglycaemia have been described, which generally respond to administration of exogenous insulin. Hyperglycaemia has been identified as an importna identified risk in the RMP.

Metabolism and nutrition disorders

An alteration in serum lipid levels was observed and changes in serum lipid values, in most cases without clinical symptoms, are very common. A rise in serum urea occurs regularly, is dose-independent and nearly always a sign of pre-renal metabolic imbalance. Hyperlipidaemia has been identified as an importna identified risk in the RMP.

General disorders and administration side conditions

Pyrexia can occur after the injection, which usually subsides spontaneously.

Hepatobiliary disorders

Alteration of liver parameters are very common. A dose-independent rise in serum transaminases, and serum bilirubin is commonly observed. Fatty liver can be observed very frequently. There have been rare reports of cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome. Impaired protein synthesis can lead to a decline in the serum proteins. There is a dose-independent decrease in serum albumin in the majority of patients during the treatment. The range of side effects of Oncaspar largely coincides with that of native non-pegylated L-asparaginase (e.g. native E. coli asparaginase). Hepatotoxicity has been identified as an important identified risk in the RMP.

Adverse events with a long latency have been included as missing information in the RMP.

Serious adverse events and deaths

From the initiation of the pegasparagase program on March 31, 1984 through to the cut-off date for this analysis of May 31, 1990, 28 serious adverse drug experiences were reported to the United States FDA. Fifteen of these reports occurred with the intravenous administration of pegasparagase during study ASP-001. Eight of these 15 reports from ASP-001 were on-study deaths due to progressive disease. These deaths were expected because at study entry the patients had life expectancies of approximately six weeks. In addition, 4 other disease-related deaths were reported for studies ASP-201A, ASP-203 and ASP-302. Thirteen other patients reported serious adverse drug experiences which included anaphylaxis, bronchospasm, convulsions, CNS haemorrhage, disorientation, pancreatitis, thrombosis, paresthesia, a systemic hypersensitivity reaction and haemolytic anaemia. None of the 10 E coli L-asparaginase patients experienced any serious adverse experiences. For Study CCG-1962, a total of five patients (4.2%) had non-fatal SAEs (3 Peg-asp patients and 2 native asp patients). The following SAEs were reported: Grade 3 or 4 coagulopathy, Grade 3or 4 pancreatitis, and Grade 4 neurologic dysfunction; foot pain; Grade 4 CNS toxicity; and Grade 3 or 4 coagulopathy and Grade 4 neurologic dysfunction.

Therefore, the SmPC section 4.3 contains contraindications for patients with hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1, history of serious thrombosis with prior L-asparaginase therapy, history of pancreatitis including pancreatitis related to prior L-asparaginase therapy (see SmPC section 4.4) and history of serious hemorrhagic events with prior L-asparaginase therapy (see SmPC section 4.4).

Hypersensitivity reactions to Oncaspar, e.g. life-threatening anaphylaxis, can occur during the therapy, particularly in patients with known hypersensitivity to the other forms of L-asparaginase. As a routine precautionary measure the patient should be monitored for an hour after administration, having resuscitation equipment and other means required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids etc.). Oncaspar should be discontinued in patients with serious allergic reactions (see sections 4.3 and 4.8). Depending on the severity of the symptoms, administration of antihistamines, corticosteroids and possibly circulation-stabilising medical product is indicated as counter-measure. Hypersensitivity has been identified as an important identified risk in the RMP.

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving Oncaspar. Oncaspar should be discontinued in patients with serious thrombotic events. Thromboembolic events have been identified as an important identified risk in the RMP.

There have been reported adverse reactions of pancreatitis. Patients should be informed of the characteristic symptom of pancreatitis that, if left untreated, could become fatal: persistent abdominal pain that could be severe, which may radiate to the back. If pancreatitis is suspected, Oncaspar should be discontinued; if pancreatitis is confirmed, Oncaspar should not be restarted. Appropriate investigations (e.g. ultrasound) should therefore be performed up to four months after termination of Oncaspar therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended. Disturbances of exocrine pancreatic function can result in diarrhoea.

Serum amylase measurements should be carried out frequently to identify early signs of inflammation of the pancreas.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia can occur in patients receiving Oncaspar. Coagulation parameters should be monitored at baseline and periodically during and after treatment; particularly when other medicinal products with coagulation-inhibiting effects such as acetylsalicylic acid and nonsteroidal anti-inflammatory medicinal products are used simultaneously (see SmPC section 4.5).

Regular monitoring of the coagulation profile is necessary. Fibrinogen can be regarded as a parameter of the pro- and anticoagulatory system. When there is a marked drop in fibrinogen or AntithrombinIII (ATIII) deficiency, consider targeted substitution (e.g. fresh frozen plasma).

Combination therapy with Oncaspar can result in severe hepatic toxicity and central nervous system toxicity.

Caution is required when Oncaspar is given in combination with other hepatotoxic substances, especially if there is pre-existing hepatic impairment. In this case, patients should be monitored for liver impairment.

Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN) is also a contraindication (see SmPC section 4.3).

In the presence of symptoms of hyperammonemia (e.g. nausea, vomiting, lethargy, irritation), ammonia levels should be monitored closely (see SmPC section 4.4).

Safety and efficacy in Philadelphia chromosome-positive patients has not been established. A possible increased risk of hepatotoxicity when combining imatinib with L-asparaginase therapy should be taken into account prior deciding to use Oncaspar in this patient population (see SmPC section 4.4).

Safety in special populations

There have been no further published cases of leucopenia following in utero exposure to L-asparaginase in the 36 years since. The two published case reports mentioned in the question pre-date pegasparagase by more than a decade. The history of commercial pegasparagase use covers more than 20 years, during which time it is estimated that almost 70,000 patients have been exposed. No case of leucopenia following in utero exposure has been reported during this period. Therefore, there is no need to include the theoretical risk of leucopenia in the SmPC. However, the applicant has updated the RMP with the 2 case reports referred to in the question and, in the event of a spontaneous case of pregnancy being reported in a patient undergoing treatment with pegasparagase, routine pharmacovigilance practice would ensure that all pregnancies are followed up and any problems with mother or foetus would be identified.

There are limited amount of data from the use of L-asparaginase and no data from the use of Oncaspar, in pregnant women. No reproduction studies in animals with pegaspargase were performed but studies in animals with L-asparaginase have shown teratogenicity (see section 5.3). Taking into account teratogenic effects of L-asparaginase observed in rat and rabbit studies and due to its pharmacological properties, Oncaspar should not be used during pregnancy unless the clinical conditions of the woman requires treatment with pegaspargase. This is in line with the guideline on risk assessment of medicinal product on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005). Teratogenicity has been identified as an important identified risk in the RMP. Effective contraception must be used during treatment and for at least 6 months after Oncaspar discontinuation. Since an indirect interaction between components of the oral contraception and pegaspargase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation (see sections SmPC 4.5 and 4.6).

Concerning the breast feeding, it is not known whether pegaspargase is excreted into breast milk. Based on its pharmacological properties any risk to the breastfed newborns/infants cannot be excluded. As a precautionary measure, breast-feeding should be discontinued during treatment with Oncaspar and should not be resumed after discontinuation of Oncaspar. The use of Oncaspar in pregnant or lactating women has been included as missing information in the RMP.

There is limited data available for patients older than 65 years. Therefore, the safety in elderly patients has been included as missing information in the RMP.

There is limited information in patients with severe liver impairment and patients with renal impairment. Therefore the safety in these patients will be closely monitored as reflected in the RMP under missing information.

Immunological events

The main described allergic AEs are urticarial, rash, dyspnea, bronchospasm, tachycardia, hypotension and anaphylactic shock. One case of toxic epidermal necrolysis (Lyell's syndrome) has been described. The overall rate of hypersensitivity reactions with pegasparagase has been reasonably stable taking in consideration the large patient exposure over 20 years. The data presented does not suggest an increase in the incidence of hypersensitivity reactions over time.

Specific antibodies to pegaspargase have been measured; uncommonly they were associated to hypersensitivity reactions. Neutralising antibody reducing clinical efficacy were also recorded. Immunogenicity has been included as a potential risk in the RMP. In addition, treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of Oncaspar. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section 4.2). Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out accelerated elimination of asparaginase activity. Low asparaginase activity levels are often accompanied by the appearance of anti-asparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. Expert advice should first be sought (see section 4.4).

Effects on ability to drive and use machines

Oncaspar may have a major influence on the ability to drive and use machines, by altering the ability to react.

Patients should be advised not to drive or operate machinery if they experience confusion or somnolence or other adverse reactions which can impair their ability to drive or operate machinery.

Overdose

There have been a few cases of overdose due to accidental mistakes reported with Oncaspar. Following overdose, increased liver enzymes, rash and hyperbilirubinaemia have been observed.

There is no specific pharmacological treatment. In case of overdose, patients must be carefully monitored for signs and symptoms of adverse reactions, and appropriately managed with symptomatic and supportive treatment.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Based on available safety data, it is concluded that the safety of pegasparagase does not differ dramatically from native asparaginase. Overall, the most common adverse reactions in the (>=20%) are hypersensitivity including anaphylactic reaction, febrile neutropenia, anaemia, hyperglycaemia platelet count decreased, neutrophil count decreased, blood bilirubin increased. The treatment of ALL patients with pegasparagase is considered to be well tolerated and the toxicities manageable, as per the recommendations stated in the SmPC and the risk minimisation measures in the RMP. Furthermore, additional safety data will be available from the two post-authorisation efficacy studies (PAES) (see discussion on clinical efficacy) and enable to further characterise the safety profile of oncaspar:

- Study CAALL-F01, a prospective multicentre cohort study evaluating Oncaspar used in the first-line treatment of children and adolescents with ALL along with multi-agent chemotherapy.
- A multicentre, open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar in adults (aged 18-60) with newly diagnosed ph negative acute lymphoblastic leukaemia.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 1.0 (dated 18 June 2014) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 06 November 2014.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 1.0 (dated 17 November 2015) with the following contents:

Safety concerns

Important identified risks	Hypersensitivity (Including severe hypersensitivity and anaphylactic shock) Pancreatitis Hyperlipidaemia Haemorrhage Thromboembolic events Hyperglycaemia Hepatotoxicity Infection Neurotoxicity Embryotoxicity and teratogenicity Interactions with anticoagulants, corticosteroids, methotrexate and cytarabine, vincristine and live vaccines, and medicines with increased toxicity due to pegaspargase induced impaired liver metabolism
Important potential risks	Immunogenicity Reversible posterior leukencephalopathy syndrome (RPLS)
Missing information	Effects on fertility Safety following IV route of administration Adverse events with a long latency Safety of patients with severe liver impairment Safety in patients with renal impairment Use in elderly patients

Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Plan

N/A

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity	SmPC text in section 4.3, 4.4, 4.5, 4.8.	Not applicable
Pancreatitis	SmPC text in section 4.3, 4.4, 4.8.	Not applicable
Hyperlipidaemia	SmPC text in section 4.8.	Not applicable
Haemorrhage	SmPC text in section 4.3, 4.4, and 4.8.	Not applicable
Thromboembolic events	SmPC text in section 4.3, 4.4, 4.5, and 4.8.	Not applicable
Hyperglycaemia	SmPC text in section 4.8	Not applicable
Hepatotoxicity	SmPC text in section 4.2, 4.4, 4.5, 4.8, and 5.3,	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infection	SmPC text in section 4.8.	Not applicable
Neurotoxicity	SmPC text in section 4.4, and 4.8.	Not applicable
Embryotoxicity and teratogenicity	SmPC text in section 4.6, and 5.3.	Not applicable
Interactions with anticoagulants, corticosteroids, methotrexate and cytarabine, vincristine and live vaccines, and medicines with increased toxicity due to pegaspargase induced impaired liver metabolism	SmPC text in section 4.5.	Not applicable
Immunogenicity	SmPC text in section 4.8, 5.2, and 5.3.	Not applicable
Reversible posterior leukencephalopathy syndrome	SmPC text in section 4.8.	Not applicable
Effects on fertility	SmPC text in section 4.6, and 5.3.	Not applicable
Safety following IV route of administration	SmPC text in section 4.2.	Not applicable
Adverse events with a long latency	SmPC text in section 4.8.	Not applicable
Safety of patients with severe liver impairment	SmPC text in section 4.2, and 5.2.	Not applicable
Safety in patients with renal impairment	SmPC text in section 4.2, and 5.2.	Not applicable
Use in elderly patients	SmPC text in section 4.2, and 5.2.	Not applicable

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The applied indication in the treatment of patients with acute lymphoblastic leukaemia (ALL) covers both first line treatment (newly diagnosed patients never treated for their disease, non-hypersensitive population) and second line treatment (patients with one relapse/treatment failure). In the context of a second line treatment, Oncaspar can be given in first intention in patients non-hypersensitive to native forms of asparaginase or in second intention, i.e. when native asparaginase cannot be used due to hypersensitivity. Clinical data were provided to support the use of Oncaspar both in hypersensitive patients and non-hypersensitive patients.

In the main study CCG-1962 to evaluate the use of Oncaspar in first line treatment of ALL (non-hypersensitive population), 118 paediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomised to Oncaspar or native E. coli L asparaginase as part of combination therapy. The pattern of asparagine depletion was quite similar in all phases of treatment, and for both asparaginases The overall 3-year, 5-year and 7-year event-free survival (EFS) were 83%, 78% and 75% in the Oncaspar group versus 79%, 73% and 66% in the native E. coli asparaginase group. This study was not specifically powered to detect event free survival (EFS) and overall survival (OS) differences between treatment groups. However, significant differences in efficacy between treatment groups can be excluded.

Supportive data were provided from a controlled, randomised study comparing Oncaspar to another pegylated asparaginase product in combination with multi-agent chemotherapy in the first line treatment of newly diagnosed patients from 1 to 30 years of age with high risk B-precursor ALL (N=166). At 3-years, the EFS and overall survival (OS) for the Oncaspar treatment arm were 85.1% [95% CI 72-92%] and 92.4% [95% CI 81-97%], respectively.

Separate pooled estimates of outcomes and events from a systematic review of all the available clinical trials in which only Oncaspar or E. coli L-Asparaginase were used in first-line were also provided to support the non-inferiority of Oncaspar compared to native E. coli asparaginase. Overall, results from all pooled analyses do not show any significant reduction in the efficacy outcomes observed when Oncaspar is used upfront. Immunogenicity data also support the use of Oncaspar in first-line.

With regards to the use of Oncaspar in second-line treatment of ALL patients, study ASP-304 was the only comparative study versus native asparaginase of the dossier and is considered the most relevant study. Complete remission rates were respectively 41% in hypersensitive patients directly assigned to Oncaspar, 39% in non-hypersensitive patients randomised under Oncaspar, and 47% in patients randomised in the asparaginase treatment arm.

Supportive data were provided from five open-label studies (ASP-001, ASP-001C/003C, ASP-201A, ASP-302, ASP-400) evaluating Oncaspar in relapse/refractory haematological diseases. Overall, in the six studies (ASP-001, ASP-001C/003C, ASP-201A, ASP-302, ASP-400, ASP-304) a total of 94 patients with ALL diagnosis with a history of prior clinical allergic reaction to native E. coli L-asparaginase (HS-ALL) were exposed to Oncaspar. One patient received Oncaspar doses of 250 and 500 Units/m^2 intravenously. The remaining patients were treated with 2000 or 2500 U/m^2 administered intramuscularly or intravenously. Patients received Oncaspar as a single agent or in combination with multi-agent chemotherapy. Overall, from five studies (ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400) analysed based on 65 ALL patients exposed to Oncaspar using the highest therapeutic response during the entire study, complete remission were observed in 30 patients (46%), partial remission in 7 patients (11%) and haematological improvement in 1 patient (2%).

In study ASP-001C/003C among the 29 hypersensitive ALL patients exposed to Oncaspar, 11 patients were evaluated for response during induction. Of these, 3 patients achieved complete remission (27%), 1 patient had partial remission (9%), 1 patient had haematologic improvement (9%) and 2 patients had therapeutic efficacy (18%). Therapeutic efficacy was defined as a clinical improvement which did not meet the criteria for other beneficial outcomes. During the maintenance phase, 19 patients were evaluated, with 17 patients achieving complete remission (89%), and 1 patient with therapeutic efficacy, (5%) (see SmPC section 5.1).

Uncertainty in the knowledge about the beneficial effects

No data are available in high risk ALL Philadelphia chromosome positive (Ph+) patients and a warning has been included in the SmPC concerning the uncertain benefit of Oncaspar in such a population.

Some uncertainties were raised with regards to ALL patients non-hypersensitive to native forms of asparaginase considering the absence of primary analysis in terms of clinical efficacy or PD to support the use of oncaspar in the first line setting (study CCG-1962). Furthermore, results obtained in non-hypersensitive patients in the second line setting from study ASP-304 indicate that the observed complete remission rates in ALL patients to native asparaginase was lower with Oncaspar than with native asparaginase (p=0.625). However, the observed CR difference lacks statistical significance, possibly due to the fact that inclusions were stopped before reaching the planned sample size.

Despite the above uncertainties, the results obtained in ALL patients non-hypersensitive to native asparaginase in study CCG-1962 in first line treatment were considered clinically relevant. In addition, further efficacy and PD data will be available in the subpopulation of patients non-hypersensitive to native asparaginase from a post-marketing efficacy study (PAES): study CAALL-F01. This trial will be conducted in paediatric patients with newly diagnosed acute lymphoblastic leukaemia (see Annex II condition).

Finally, since most of the studies presented were conducted in children, adolescents and young adults, there are only limited data available in the adult population. A post-authorisation efficacy study (PAES) investigating safety and efficacy when PEG-ASP is used in the first-line treatment along with multi-agent chemotherapy in adults with ALL will provide relevant efficacy data in this subpopulation (see Annex II conditions). This trial will also allow collecting further data to characterise the efficacy of Oncaspar in patients non-hypersensitive to asparaginase.

Risks

Unfavourable effects

Overall, the most frequent adverse events observed in second-line use studies (except immunological events) were hyperbilirubinemia, increased SGPT/SGOT, decreased albumin, hyperproteinaemia, fatty liver, hyperamylaseamia, decreased fibrinogen, increased partial thromboplastin time, central nervous system thrombosis. Other adverse events (less frequent) were nausea, vomiting, diarrhoea, chills, fever, peripheral neuritis and pain in extremity.

The most frequently occurring toxicities in the main study (ASP-304) in the second line setting were hepatotoxicity and coagulopathy, the majority of which were laboratory abnormalities without clinical manifestations. An examination of the expended toxicological data showed a high incidence of hypoproteinaemia observed during induction therapy in the treatment groups. There was no incidence of bleeding disorders or increased creatinine in any of the treatment groups.

Thirty-three (83%) of 40 patients directly assigned to Oncaspar had a total of 75 drug related adverse experiences with an average duration of 13.5 days. The most common (greater than five percent) oncaspar related adverse experiences were increased SGPT (45%), hypoproteinemia

(40%), decreased fibrinogen (30%), increased partial thromboplastin time (15%), hyperbilirubinemia (15%), and fever (8%) and allergic reactions.

Overall, the incidences and types of toxic events in studies in first line setting were very similar between PEG-ASNase and native E.coli ASNase arms. Infections were the most toxic events. CNS thrombosis occurred in the PEG-ASNase treatment, once during induction and on the second Day 22 of delayed intensification #1. There was one event of pancreatitis in each arm during induction. There were two additional occurrences of pancreatitis in the PEG-ASNase group and during delayed intensification #2.

28 serious adverse drug experiences were reported while the product was in the US market. In study CCG-1962, a total of five patients (4.2%) had non-fatal SAEs (3 pegaspargase patients and 2 native asparaginase patients). Grade 3 or 4 coagulopathy, Grade 3 or 4 pancreatitis, and Grade 4 neurologic dysfunction; foot pain; Grade 4 CNS toxicity; and Grade 3 or 4 coagulopathy and Grade 4 neurologic dysfunction were reported.

Uncertainty in the knowledge about the unfavourable effects

The submitted safety data were taken from a limited number of well-designed and/or up to date studies. Therefore, the safety database is considered limited and no long term safety data was available. The safety profile of Oncaspar will be closely monitored through routine pharmacovigilance as reflected in the RMP.

Balance

Importance of favourable and unfavourable effects

The endpoints of complete remission after induction and the pharmacodynamics data (asparagine blood levels) were considered as acceptable main efficacy endpoints.

Results of study ASP-304 show that, in ALL hypersensitive patients in second relapse, Oncaspar treatment induced a complete remission rate of 41% as part of the induction regimen. These results are considered clinically relevant, especially taking into consideration that hypersensitive patients cannot be retreated with the native E coli asparaginase. Furthermore, the results obtained in ALL patients non-hypersensitive to native asparaginase in study CCG-1962 are considered clinically relevant.

Although the safety can be considered established, albeit based on a limited safety database, further measures stated in the RMP will ensure that further safety data will be collected in adults and in patients non-hypersensitive to native asparaginase.

Benefit-risk balance

Taking into account the efficacy of PEG-asparaginase in terms of serum asparagine depletion and complete response rate, and the safety of Oncaspar, the Benefit/Risk balance of Oncaspar is considered positive in the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients, as a component of antineoplastic combination therapy.

Discussion on the benefit-risk assessment

The initial proposed indication by the applicant included all ALL treatment phases (induction-consolidation/intensification-maintenance). It was considered debatable that the reported use of Oncaspar in the interim-maintenance phases, which are limited in time and interspersed between more intensive treatment phases, truly qualified as maintenance treatment. Therefore, the indication wording not referring to maintenance phase but more generally to the use of Oncaspar as a component of antineoplastic combination therapy is considered acceptable.

There were uncertainties in the use of Oncaspar in patient who are not hypersensitive to native asparaginase (i.e. use in first intention) due to the limitations of the data provided in the first line and second line setting. In particular, study CCG-1962 was not specifically powered to detect event free survival (EFS) and overall survival (OS) differences between treatment groups. However, the observed efficacy results were adequate.

Results from study CAALL-F01, investigating safety and efficacy of Oncaspar used in the first-line treatment along with multi-agent chemotherapy in children with ALL, will allow to further characterise the benefit/risk balance of Oncaspar in patients who are not hypersensitive to native asparaginase (see Annex II conditions).

Finally, most of the trials were performed in children, adolescents and young adults. However, asparaginase has been shown to have a benefit in ALL adult patients based on literature data and clinical experience. Therefore, the CHMP does not recommend a restriction concerning the use of Oncaspar according to age. However, additional data are necessary to further define the efficacy, safety and immunogenicity of Oncaspar in adults and will be available from a clinical study evaluating Oncaspar in adults with newly diagnosed Philadelphia chromosome negative acute lymphoblastic leukaemia (see Annex II conditions).

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Oncaspar is not similar to Atriance (nelarabine), Evoltra (clofarabine), Iclusig (ponatinib), Xaluprine (mercaptopurine), Sprycel (dasatinib) and Blincyto (blinotumomab) within the meaning of Article 3(3)(b) of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Oncaspar as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in patients with newly diagnosed acute lymphoblastic leukaemia, the MAH should submit the results of Study CAALL-F01, a prospective multicentre cohort study evaluating Oncaspar used in the first-line treatment of children and adolescents with ALL along with multi-agent chemotherapy. The clinical study report should be submitted by:	December 2025
Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in adult patients with ALL, the MAH should submit the results of a multicenter, open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar in adults (aged 18-60) with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukemia. The clinical study report should be submitted by:	December 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.