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FDA Drug Approval Summary: Pegaspargase (Oncaspar®) for the First-Line Treatment of Children with Acute Lymphoblastic Leukemia (ALL)

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Key Words. Pegaspargase • Oncaspar® • Pediatric ALL

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the effect of pegylation on asparaginase pharmacokinetics and immunogenicity.
2. Identify the current pegaspargase indications.
3. Discuss the advantages of pegaspargase treatment.
4. Outline the clinical trial design leading to pegaspargase approval by the FDA.
5. List the major adverse events associated with pegaspargase treatment.

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ABSTRACT

On July 24, 2006, the U.S. Food and Drug Administration granted approval to pegaspargase (Oncaspar®; Enzon Pharmaceuticals, Inc., Bridgewater, NJ; hereafter, O) for the first-line treatment of patients with acute lymphoblastic leukemia (ALL) as a component of a multiagent chemotherapy regimen. O was previously approved in February 1994 for the treatment of patients with ALL who were hypersensitive to native forms of L-asparaginase.

The trial supporting this new indication was an open label, randomized, multicenter clinical trial that enrolled 118 children (age, 1–9 years) with previously untreated, standard risk ALL. Patients received either native *Escherichia coli* asparaginase (Elspar®; Merck, Whitehouse Station, NJ; hereafter, E) or O along with

multiagent chemotherapy during remission induction and delayed intensification (DI) phases of treatment. O, at a dose of 2,500 IU/m², was administered i.m. on day 3 of the 4-week induction phase and on day 3 of each of two 8-week DI phases. E, at a dose of 6,000 IU/m², was administered i.m. three times weekly for nine doses during induction and for six doses during each DI phase. This study allowed direct comparison of O and E for asparagine depletion, asparaginase activity, and development of asparaginase antibodies. An unplanned comparison of event-free survival (EFS) was conducted to rule out a deleterious O efficacy effect.

Following induction and DI treatment there was complete ($\leq 1 \mu\text{M}$) or moderate (1–10 μM) depletion of serum asparagine levels in the large majority of samples

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tested over the 4-week period in both O-treated and E-treated subjects.

Similarly, depletion of cerebrospinal fluid asparagine levels during induction was similar between O-treated and E-treated subjects.

The number of days asparaginase activity exceeded >0.03 IU/ml in O-treated subjects was greater than the number of days in E-treated subjects during both the induction and DI phases of treatment. There was no correlation, however, between asparaginase activity and serum asparagine levels, making the former determination less clinically relevant.

Using the protocol-prespecified threshold for a positive result of >2.5 times the control, 7 of 56 (12%) O

subjects tested at any time during the study demonstrated anti-asparaginase antibodies and 16 of 57 (28%) E subjects tested at any time during the study had anti-asparaginase antibodies. In both study arms EFS was in the range of 80% at 3 years.

The most serious, sometimes fatal, O toxicities were anaphylaxis, other serious allergic reactions, thrombosis (including sagittal sinus thrombosis), pancreatitis, glucose intolerance, and coagulopathy. The most common adverse events were allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases. *The Oncologist* 2007;12:991–998

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Asparaginase was identified as a potential chemotherapeutic agent in 1961 when it was isolated as an antilymphoma component of guinea pig serum [1]. Consecutive series of clinical trials testing this agent in children with acute lymphoblastic leukemia (ALL) confirmed its importance as a component of therapy for childhood ALL [2–6]. In the U.S. there are two forms of commercially available asparaginase: Elspar® (hereafter, E), an *Escherichia coli*-derived asparaginase manufactured by Merck (Whitehouse Station, NJ), and pegaspargase (Oncaspar®; hereafter, O), a pegylated form of asparaginase, manufactured by Enzon Pharmaceuticals, Inc. (Bridgewater, NJ) from the Merck asparaginase bulk drug product.

Pegylation, the technology of polyethylene glycol covalent conjugation to a biopharmaceutical, increases the drug hydrodynamic radius, prolongs plasma retention time, decreases proteolysis, decreases renal excretion, and shields antigenic determinants from immune detection without obstructing the substrate-interaction site [7].

O, produced by covalent conjugation of monomethoxypolyethylene glycol (PEG) to native L-asparaginase, was approved in 1994 for use in ALL patients who developed hypersensitivity to the native form of asparaginase. This supplemental application requests that the indication statement for O be revised to include an additional indication for the initial therapy of patients with ALL.

The standard dosing schedule of E is 6,000 IU/m² three times weekly for nine doses during remission induction and for six doses during delayed intensification. Administration of an equivalent antileukemic dose of pegylated asparaginase as one injection rather than six or nine injections would

represent an important improvement in the morbidity of treatment for most children with ALL.

The Children's Cancer Group (CCG) conducted a study in children with standard-risk ALL to compare the pharmacokinetics, pharmacodynamics, immunogenicity, and pharmacoeconomics of pegylated versus native asparaginase administered as described above [8, 9]. Event-free survival (EFS) was also analyzed to assess whether O treatment had a possible detrimental effect.

PATIENTS AND METHODS

The primary efficacy study was a randomized, open-label, pharmacodynamic, and pharmacokinetic, phase II study, conducted at six U.S. CCG institutions, in patients with standard-risk ALL (subset of ALL defined by characteristics that are identified at diagnosis, such as age and white count, as well as additional factors that are identified later, such as initial response to therapy [day 14 marrow] and the absence of specific cytogenetic abnormalities [primarily Philadelphia chromosome]). Subjects entered in the study who were subsequently identified as having factors designating a higher risk category were removed from the study and treated with therapy appropriate for their risk category.

Eligibility criteria included newly diagnosed previously untreated ALL, age 1–9 years, initial WBC at a treating institution of $<50,000/\mu\text{l}$, and $\leq 25\%$ L3 blasts.

Patients with massive lymphadenopathy, massive splenomegaly, and/or a large mediastinal mass at diagnosis were eligible as were patients with central nervous system (CNS) or testicular leukemia.

Remission induction/consolidation treatment included intrathecal ara-C and methotrexate, vincristine, prednisone, 6-mercaptopurine, and methotrexate with either E or O. Delayed intensification therapy included in-

Table 1. Demographic and baseline characteristics

	E (n = 59)	O (n = 59)
Age, n (%)		
1–2 years	11 (19)	20 (34)
3–5 years	26 (44)	18 (31)
6–9 years	22 (37)	21 (36)
Sex, n (%)		
Male	31 (53)	33 (56)
Female	28 (47)	26 (44)
Race, n (%)		
White	38 (64)	39 (66)
Nonwhite	21 (36)	20 (34)
WBC at diagnosis, n (%)		
<20,000/ μ l	47 (80)	46 (78)
>20,000/ μ l	12 (20)	13 (22)
CALLA+ (reactive to common ALL antigen), n (%)	50 (85)	53 (90)
Platelet count at diagnosis, n (%)		
<50,000/ μ l	20 (34)	30 (51)
50,000–149,000/ μ l	21 (36)	19 (32)
>150,000/ μ l	18 (31)	10 (17)
Hemoglobin level, n (%)		
<8 g/dl	30 (51)	24 (41)
8–11 g/dl	23 (39)	29 (49)
>11 g/dl	6 (10)	6 (10)
Central nervous system disease (cerebrospinal fluid sample), n (%)		
>5 WBCs/ μ l, positive cytology (blasts)	—	—
<5 WBCs/ μ l, positive cytology (blasts)	4 (7)	9 (15)
>5 WBCs/ μ l, negative cytology	1 (2)	4 (7)
<5 WBCs/ μ l, negative cytology	51 (86)	42 (71)
Mediastinal mass less than one third thoracic diameter, n (%)	4 (7)	6 (10)
Hepatomegaly, edge below the umbilicus, n (%)	4 (7)	2 (3)
Splenomegaly, edge below the umbilicus, n (%)	3 (5)	3 (5)
Lymphadenopathy, massive, n (%)	1 (2)	1 (2)

Abbreviations: ALL, acute lymphoblastic leukemia; E, native *Escherichia coli* asparaginase; O, pegaspargase.

trathecal methotrexate, vincristine, dexamethasone, doxorubicin, cyclophosphamide, ara-C, thioguanine, and either E or O.

Serum (5 ml red top tube) for asparagine concentration, asparaginase levels, and asparaginase antibodies was obtained before the first dose of asparaginase and on days 7, 14, 21, and 28 of induction therapy and on days 0, 7, 14, 21, and 28 of delayed intensification. Asparagine concentration in cerebrospinal fluid (CSF) (1–2 ml spinal fluid) was determined from samples obtained at the initial spinal tap and from induction day 7 and 28 spinal taps.

O (2,500 IU/m²) was administered i.m. on day 3 of the remission induction and delayed intensification phases of treatment. E (6,000 IU/m²) was administered i.m. on day 3 then Monday, Wednesday, and Friday for a total of nine doses during remission induction and on day 3 then Monday, Wednesday, and Friday for a total of six doses during each delayed intensification cycle.

The stated objective regarding asparagine levels in the CCG phase II study was to compare the duration of time serum asparagine levels were <1 μ M for O-treated subjects with the duration in E-treated subjects during induction and

Table 2. Number of subjects with samples evaluated for asparagine and asparaginase levels

Arm	Potential	% Samples tested	n of subjects with any samples	% 4 or 5 samples
Induction				
O	$58 \times 5 = 290$	$252/290 = 87\%$	58	79%
E	$59 \times 5 = 295$	$256/295 = 87\%$	57	81%
Delayed intensification 1				
O	$55 \times 5 = 275$	$191/275 = 69\%$	53	58%
E	$52 \times 5 = 260$	$203/260 = 78\%$	48	69%
Delayed intensification 2				
O	$50 \times 5 = 250$	$191/250 = 76\%$	47	66%
E	$48 \times 5 = 240$	$188/240 = 78\%$	46	68%

Abbreviations: E, native *Escherichia coli* asparaginase; O, pegaspargase.

delayed intensifications 1 and 2. This is somewhat different from the Berlin-Frankfort-Munich (BFM) group criteria that uses the following asparagine depletion grading system: $\leq 0.1 \mu\text{M}$, complete depletion; >0.1 to $\leq 0.5 \mu\text{M}$, nearly complete depletion; >0.5 to $\leq 1 \mu\text{M}$, moderate reduction; >1 to $\leq 40 \mu\text{M}$, slight reduction; $>40 \mu\text{M}$, no reduction [10].

The stated objective regarding asparaginase activity was to compare the duration of time serum asparaginase activity would remain >0.03 IU/ml for O-treated subjects with the duration in E-treated subjects during induction and delayed intensifications 1 and 2. The threshold of >0.03 IU/ml is based on data indicating that this level of asparaginase activity results in undetectable levels of asparagine [11, 12]. An alternative threshold of >0.1 IU/ml has been used in studies of asparaginase conducted by the BFM group [13, 14] because activity above this threshold has been postulated to be sufficient to result in adequate asparagine depletion in plasma and CSF [15]. A more recent review of the pharmacokinetic and pharmacodynamic properties of asparaginase formulations concluded that therapeutically effective depletion of asparagine is achieved with serum asparaginase activity levels ≥ 0.4 – 0.7 IU/ml in newly diagnosed ALL patients [16].

The development of a humoral immune response (anti-asparaginase antibodies) against O or E was determined using an enzyme-linked immunosorbent assay method. A positive result was defined as any postexposure measurement that was $>2.5\times$ the control.

Safety data focused on known and prespecified asparaginase toxicities. Because there are decades of experience with asparaginase in this patient population and the toxicities of asparaginase are well known, this approach was expected to adequately compare the O and E toxicity profiles. Toxicity information was collected during remission induction and delayed intensification 1 and 2, the treatment phases that included asparaginase treatment.

RESULTS

Demographics and baseline disease characteristics of study patients are summarized in Table 1. The demographic and baseline characteristics of subjects assigned to the two study arms were similar except that the E arm had a higher percentage of subjects aged 1–2 (34% versus 19%), a higher percentage of subjects with platelet counts $<50,000/\mu\text{l}$ (51% versus 34%), and a higher percentage of subjects with equivocal CNS disease (15% versus 7%).

Table 3. Cerebrospinal fluid asparagine depletion during induction

	Pre-Asp Rx		Day 7 (day 4 post-Asp)		Day 28 (day 25 post-Asp)	
	Mean	Median	Mean	Median	Mean	Median
O	$3.1 \mu\text{M}$	$2.56 \mu\text{M}$	$1.7 \mu\text{M}$	$1.17 \mu\text{M}$	$1.5 \mu\text{M}$	$0.61 \mu\text{M}$
<i>n</i> = 50	37		33		30	
E	$3.3 \mu\text{M}$	$2.76 \mu\text{M}$	$1.6 \mu\text{M}$	$1.06 \mu\text{M}$	$0.7 \mu\text{M}$	$0.09 \mu\text{M}$
<i>n</i> = 49	40		34		28	

Abbreviations: Asp, asparaginase; E, native *Escherichia coli* asparaginase; O, pegaspargase; Rx, treatment.

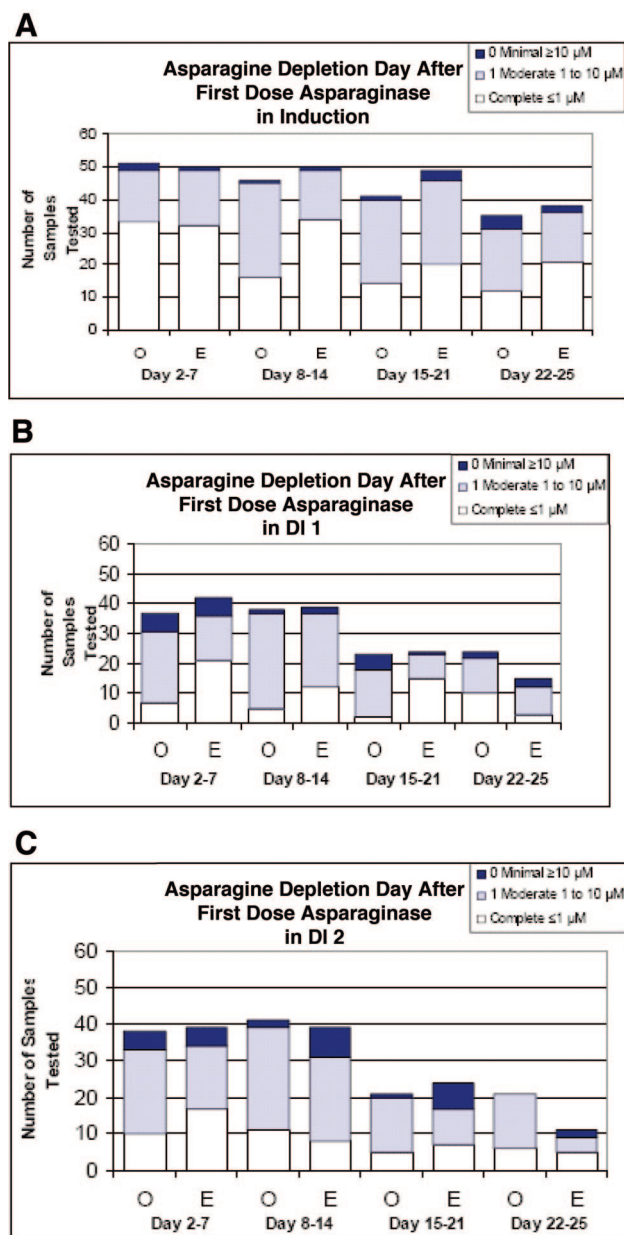


Figure 1. Asparagine depletion after the first dose of asparaginase in the induction (A) and intensification 1 (B) and 2 (C) phases of the study.

Abbreviations: DI, delayed intensification; E, native *Escherichia coli* asparaginase; O, pegaspargase.

Serum or CSF Asparagine Depletion

Table 2 summarizes the number of subjects with serum samples evaluated for asparagine and asparaginase levels. As seen, more than half the samples specified in the protocol to examine asparagine and asparaginase levels were obtained, although most of these samples were not drawn on the protocol-specified day.

Figure 1A-C summarizes asparagine depletion resulting from O and E induction and delayed intensification 1 and 2

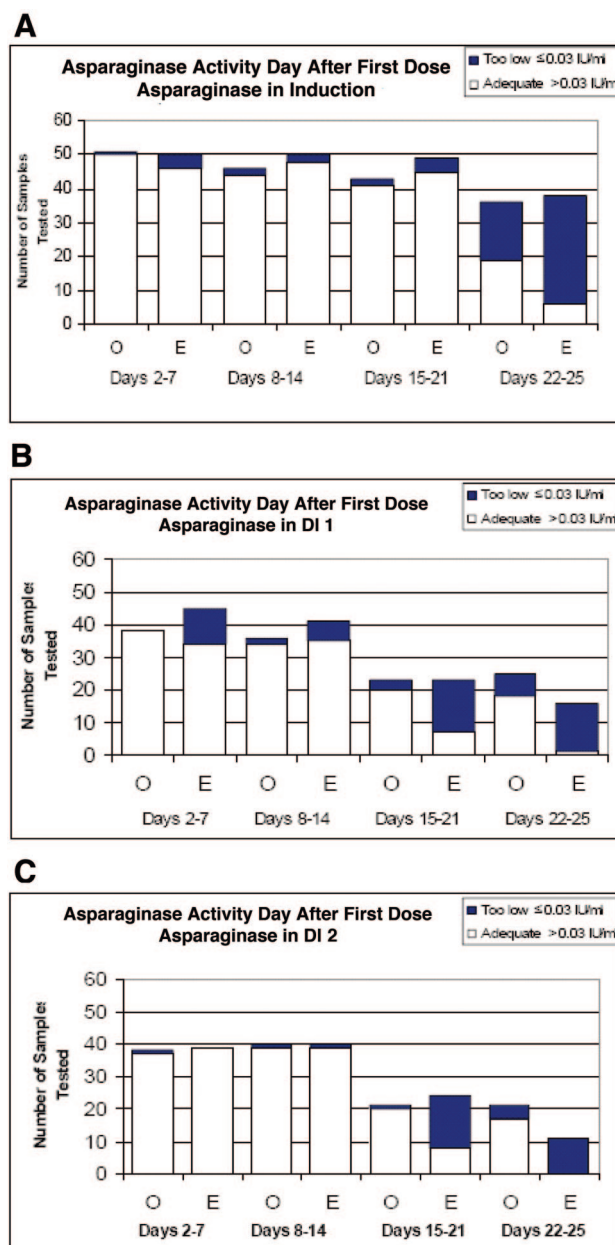


Figure 2. Proportion of samples with asparaginase activity $\geq 0.03 \text{ IU/ml}$ in the induction (A) and intensification 1 (B) and 2 (C) phases of the study. Blue, asparaginase activity too low ($< 0.03 \text{ IU/ml}$).

Abbreviations: DI, delayed intensification; E, native *Escherichia coli* asparaginase; O, pegaspargase.

treatment. As indicated, O and E seem relatively comparable regarding asparagine depletion (nearly complete or moderate) during remission induction and delayed intensification.

CSF asparagine values during remission induction are summarized in Table 3. Samples were collected ± 1 day of the specified collection day. Both O and E caused a decrease in CSF asparagine values to $< 1 \mu\text{M}$ by day 28 of the treatment cycle.

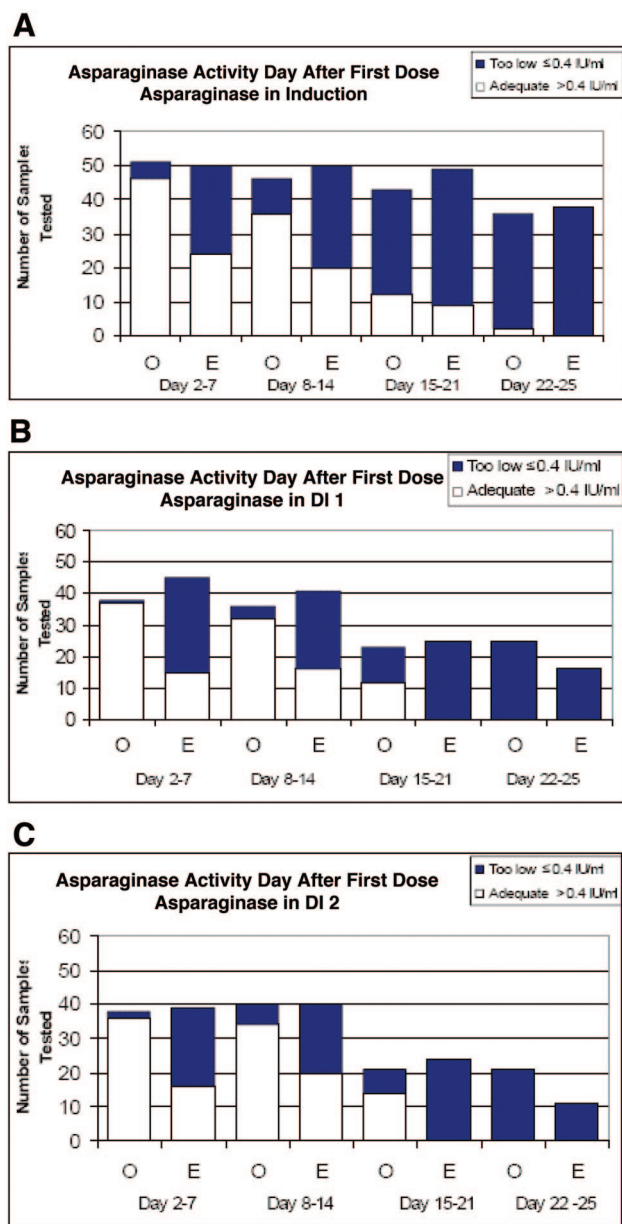


Figure 3. Proportion of samples with asparaginase activity ≥ 0.4 IU/ml in the induction (A) and intensification 1 (B) and 2 (C) phases of the study.

Abbreviations: DI, delayed intensification; E, native *Escherichia coli* asparaginase; O, pegaspargase.

Asparaginase Activity

Figure 2A–C and Figure 3A–C summarize the proportion of samples, at specified time points during induction or delayed intensification, that either had asparaginase activity >0.03 IU/ml (Fig. 2A–C) or >0.4 IU/ml (Fig. 3A–C). Using either threshold, O maintained adequate asparaginase activity over a longer time period than E. Comparing Figure 1A–C with either Figure 2A–C or Figure 3A–C, it appears that serum asparaginase level did not correlate with serum asparagine depletion, especially toward the end of the in-

duction or intensification cycles, as serum asparagine remained depleted despite declining concentrations of asparaginase.

Asparaginase Immunogenicity

Overall, 7 of 56 (12%) O-treated subjects and 16 of 57 (28%) E-treated subjects tested at any time during the study demonstrated anti-asparaginase antibodies as defined in the protocol ($>2.5\times$ the control values). Excluding the three subjects with anti-asparaginase antibody present prior to exposure to asparaginase, 6 of 55 (11%) O-treated subjects and 14 of 55 (25%) E-treated subjects tested at any time during the study demonstrated anti-asparaginase antibodies. Using the Fisher's exact test, the incidence of antibody as defined in the protocol ($>2.5\times$ control) was significantly less during induction in the O-treated subjects than in the E-treated subjects ($p = .003$). There was no significant difference between treatment groups across all treatment phases using the Cochran-Mantel-Haenszel test.

EFS

This study was not powered to analyze the superiority or noninferiority of O compared with E on EFS or survival. Using an intent-to-treat analysis with a median follow-up of 3.2 years, the 3-year EFS rates were approximately 80% in both arms.

Safety

There were 118 subjects enrolled and randomized 1:1 to O or to E (59 per arm). Forty-eight O-treated subjects received the three planned O doses, six received two doses, four received only one dose, and one was not treated. Fifty-seven E-treated subjects received all induction E doses; one patient received seven of nine doses because of decreased fibrinogen and another patient received six of nine doses (thrombotic event). Fifty-one patients received all delayed intensification 1 E doses and one patient received two of six doses. Forty-nine patients received all six delayed intensification 2 E doses and one patient received four of six doses. There were no treatment-related deaths in this study.

Prespecified grade 3 and 4 adverse reactions occurring in O and E patients are summarized in Table 4. Clinical allergic reactions were reported in 2 O-treated patients. One patient experienced a grade 1 allergic reaction and the other grade 3 hives; both occurred during the first delayed intensification phase of the study.

DISCUSSION

The study was not designed to show superiority or noninferiority for clinical outcome. It was a phase II study that

Table 4. Per-patient incidence of selected grade 3 and 4 adverse reactions

	O (n = 58)	E (n = 59)
Abnormal liver tests	3 (5%)	5 (8%)
Elevated transaminases	2 (3%)	4 (7%)
Hyperbilirubinemia	1 (2%)	1 (2%)
Hyperglycemia	3 (5%)	2 (3%)
Central nervous system thrombosis	2 (3%)	2 (3%)
Coagulopathy	1 (2%)	3 (5%)
Pancreatitis	1 (2%)	1 (2%)
Clinical allergic reactions to asparaginase	1 (2%)	0
Abbreviations: E, native <i>Escherichia coli</i> asparaginase; O, pegaspargase.		

compared pharmacokinetic, pharmacodynamic, and immunogenicity endpoints in subjects with standard-risk ALL during the phases of therapy that included asparaginase treatment. The rationale for this approach is that the anti-leukemia mechanism of action of asparaginase has been well characterized as asparagine depletion. Although asparagine is not an essential amino acid in humans, it is an essential amino acid for some ALL lymphoblasts. Depletion of the endogenous asparagine pool results in cell death of ALL lymphoblasts.

O is a modified version of E, produced by covalent conjugation of PEG to L-asparaginase. O is approved for use in ALL patients who have become hypersensitive to E. In addition to circumventing hypersensitivity to E, pegylation results in an enzyme with a longer half-life than E. In most ALL protocols, E is given three times weekly for six or nine doses. Because of the longer half-life of O,

it is possible to achieve adequate asparagine depletion with fewer injections.

The study endpoint of interest to the U.S. Food and Drug Administration was asparagine depletion. Demonstration of a similar pattern and degree of asparagine depletion was considered a valid surrogate endpoint for clinical benefit so long as there was no indication of loss of clinical activity as determined by EFS.

Serum asparagine levels decreased after the first dose of either asparaginase preparation and remained low for approximately 3 weeks. The degree and duration of asparagine depletion was similar in O-treated and E-treated subjects. The depletion of CSF asparagine levels during induction was also similar between O-treated and E-treated subjects.

This study was not powered to analyze the effect of O compared with E on EFS or survival. With a median follow-up of 3.2 years, the 3-year EFS rates were approximately 80% in both arms, however, suggesting that O use will not compromise efficacy.

Immunogenicity of asparaginase preparations remains a clinical issue. Further evaluation of the incidence and clinical significance of the development of anti-asparaginase antibodies will be a postmarketing commitment.

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The views expressed are the result of independent work and do not necessarily represent the views and findings of the U.S. Food and Drug Administration.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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