ALL-269: Safety and pharmacokinetics of calaspargase pegol in adults with newly diagnosed Philadelphia-negative acute lymphoblastic leukemia: a phase 2/3 study

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Abstract: CONTEXT: Asparaginase remains an important component in many adult regimens for acute lymphoblastic leukemia (ALL). In pediatric patients (<21 years), calaspargase pegol (Cal-PEG) provides sustained asparagine depletion as compared to pegaspargase, with similar rates of complete remission (CR), minimal residual disease (MRD), event-free survival (EFS), and OS, with a similar safety profile. OBJECTIVE: To confirm the recommended dose of Cal-PEG in adults (age ≥22 years) and to establish safety and PK/PD analysis. DESIGN: Multicenter, phase 2/3 study (NCT04817761) assessing safety and anti-leukemic activity of Cal-PEG. Part 1 enrollment commenced Q3 2021 and will establish the safety of Cal-PEG in four groups: patients age 22-39, 40-54, and ≥55, and patients with an elevated BMI >35 kg/m2. A minimum of 4 (initial cohort) and ~8 patients will be enrolled per group. The study will be conducted in ≤25 investigational centers in the US. Part 2 will comprise expansion cohorts after verifying safety and PK/PD analysis. PATIENTS: Newly-diagnosed patients with Philadelphia-negative B- or T-cell ALL ≥22 years with ECOG performance status 0-2, no known history of pancreatitis, coagulopathy, CNS thrombosis or severe hepatic impairment. Approximately 114-122 patients are expected to be enrolled in the study, including 16-32 patients in Part 1. INTERVENTIONS: Starting doses of Cal-PEG will be based on the patients' age and BMI, with older patient groups assigned to lower doses. Patients age ≥22-39 and 40-<55 will receive Cal-PEG 2000 and 1500 U/m2, respectively. Patients with BMI >35 kg/m2 and those age ≥55 will receive 1000 U/m2. A total of 6 Cal-PEG doses will be administered during the treatment period as part of a multiagent chemotherapy regimen based on CALGB 10403, with end-of-treatment visit 1 year after the induction dose, and an additional 2 years of survival follow-up. MAIN OUTCOMES MEASURES: The primary endpoints in part 1 are the safety of Cal-PEG, incidence of pre-defined unacceptable toxicities within 30 days after the induction dose and achieving plasma asparaginase activity ≥0.1 U/mL 21 days after the consolidation day 43 dose. Secondary endpoints include immunogenicity; CR; end-of-induction and consolidation MRD; and 1-, 2- and 3-year EFS, disease-free survival, and OS.

PART 1 STUDY OBJECTIVES

- To confirm the recommended dose of calaspargase pegol (Cal-Peg) in adults (aged ≥22 years) for part 2.
- To establish the safety, efficacy, and pharmacokinetics / pharmacodynamics of Cal-Peg.

Part 2 primary objectives: To evaluate the safety of Cal-Peg in adults and the nadir plasma asparaginase activity (NPAA) as a surrogate of efficacy (NPAA level ≥0.1 U/mL 21 days after the consolidation day 43 dose).

BACKGROUND

Asparaginase

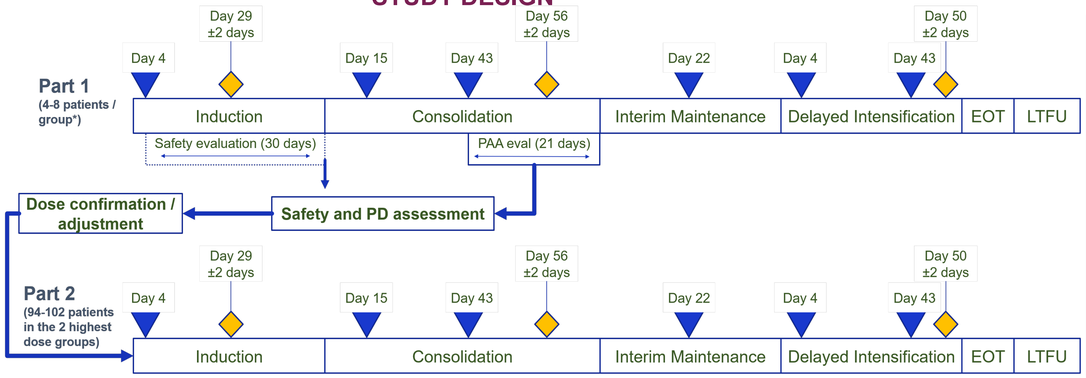
- Asparaginase (ASP) is a critical component of multi-agent chemotherapy for ALL,[1] whereby addition of ASP to standard backbone therapy results in 34%-53% higher survival rates.[2]
- Adolescents and young adults (AYA) (up to age 39) when treated with pediatric-inspired regimens containing PEGylated asparaginase (PEG-ASP) have improved event-free survival (EFS) and overall survival (OS), with comparable safety outcomes.[2-4]
- Adults aged >40 years have also had improved outcomes from pediatric-like regimens, with a manageable toxicity profile.[2,4,5]

Cal-PEG vs PEG-ASP

	PEG-ASP	Cal-PEG
ASP type	Pegylated *E. coli* asparaginase	Pegylated *E. coli* asparaginase
Linker	Succinimidyl succinate	Succinimidyl carbonate (shorter and more stable)
Half-life	~5.3 days	16.1 days
ASP activity	~3 weeks	>3 weeks
Dosing	No more than every 2 weeks	No more than every 3 weeks
Shelf life	8 months	36 months

- In pediatric populations, Cal-PEG (2500 U/m^2) and Peg-ASP (2500 U/m^2) resulted in similar efficacy outcomes for minimal residual disease (MRD), complete remission (CR) and survival outcomes (ie, EFS, disease-free survival (DFS), and 4-year OS.[6,7]
- Plasma asparaginase activity (PAA) levels were ≥0.1 U/mL 25 days after the induction dose in 95% of Cal-PEG patients vs 28.6% of PEG-ASP patients.[7]

STUDY DESIGN



Plasma asparaginase activity (PAA) and TDM monitoring

	PAA	TDM (results in 5 days)
Induction phase	Pre-dose; 24- and 48-hours post-dose	7, 14, and 21 days post-dose
Post-induction phase	Pre-dose; 24 hours post dose	7, 14, and 21 days post each dose

KEY ELIGIBILITY CRITERIA

Inclusion

- Aged ≥22 years with newly-diagnosed and cytologically confirmed and documented Philadelphia-negative B-cell or T-cell ALL by World Health Organization (WHO) classification (2016)
- Eastern Cooperative Oncology Group performance status 0-2
- No prior therapy for ALL before signing the informed consent except for limited treatment (≤7 days) with corticosteroids or hydroxyurea and a single dose of intrathecal cytarabine
- Adequate renal function (assessed within 7 days prior to inclusion): creatinine clearance ≥50 mL/min, assessed as GFR using the MDRD or Cockcroft & Gault formula.

Exclusion

- Philadelphia chromosome positive ALL, Burkitt's leukemia, mixed lineage/mixed phenotype acute leukemia, and acute undifferentiated leukemia per WHO classification
- Down syndrome
- Hepatitis B (positive for HBs antigen) and Hepatitis C (HCV antibody) at inclusion
- Known HIV positivity
- History of non-gallstone-related pancreatitis
- Severe hepatic impairment: direct bilirubin >3x upper limit of normal (ULN) or transaminases (ALT/AST) > 5x ULN (unless suspected leukemic involvement of the liver)
- History of coagulopathy
- Active thromboembolic event(s) or history of CNS thromboses

PART 1 STARTING DOSES

Patient Group	Cal-PEG Dose	Planned No. of Patients / Group
22-39 years	2000 U/m^2	4-8
40 to <55 years	1500 U/m^2	4-8
<55 years + BMI >35 kg/m^2	1000 U/m^2	4-8
≥55 years	1000 U/m^2	4-8

PART 1 ENDPOINTS

Primary endpoints

- Safety, including the incidence of unacceptable toxicities 30 days after the induction dose
- PAA profiles, including achieving PAA ≥0.1 U/mL at pre-specified time points

Secondary endpoints

- Immunogenicity
- End-of-induction MRD status
- Complete remission
- PK
- 1-year, 2-year, & 3-year EFS*, DFS*, and OS*

Exploratory endpoints

- End of consolidation MRD status for patients who are MRD positive at the end of the induction phase
- Biomarker assessment: Glutamine and derivatives

*Definitions:

- **EFS:** Time from the first dose of calaspargase pegol to the date of induction failure, documented relapse, diagnosis of a second malignant neoplasm (including myelodysplastic syndrome), or death from any cause, whichever comes first.
- **DFS:** Time from achievement of CR to the documented relapse, diagnosis of a second malignant neoplasm or death for subjects who achieve a CR.
- **OS:** Time from the first dose of calaspargase pegol to death from any cause.

CURRENT STATUS

Part 1 is currently enrolling at 10 participating centers in the US, with an enrollment of up to 122 patients expected for both parts of the study

Full treatment regimen: Remission induction therapy: Day 1 cytarabine 70 mg intrathecal; days 1-7,15-21 dexamethasone 5 mg/m^2 PO or IV BID; days 1, 8,15, 22 vincristine 1.5 mg/m^2 IV (max dose 2 mg); Days 1,8,15,22 daunorubicin 25 mg/m^2 IV; days 4 calaspargase pegol 1000-2000 U/m^2 IV; days 8,29 methotrexate 15 mg intrathecal (also administered on days 15, 22 for patients with CNS3). **Remission consolidation therapy:** Days 1,29 cyclophosphamide 1000 mg/m^2 IV; days 1-4,8-11,29,36-39 cytarabine 75 mg/m^2 IV or SC; days 1-14, 29-42 6-mercaptopurine 60 mg/m^2 orally; days 15,22,43,50 vincristine 1.5 mg/m^2 IV (max dose 2 mg); days 15,43 calaspargase pegol 1000-2000 U/m^2 IV; days 1,8,15,22 methotrexate 15 mg intrathecal (omit doses on days 15,22 for patients with CNS3). **Interim Maintenance Therapy:** Days 1,11,21,31,41 methotrexate at a starting dose of 100 mg/m^2 IV escalated by 50 mg/m^2/dose; days 1,11,21,31,41 vincristine 1.5 mg/m^2 IV (max dose 2 mg); day 22 calaspargase pegol 1000-2000 U/m^2 IV; days 1,31 methotrexate 15 mg intrathecal. **Delayed Intensification Therapy:** Days 1,8,15,43,50 vincristine 1.5 mg/m^2 IV (max dose 2 mg); days 1-7,15-21 dexamethasone 5 mg/m^2 PO or IV BID; days 1,8,15 doxorubicin 25 mg/m^2 IV; days 4 (or 5 or 6),43 calaspargase pegol 1000-2000 U/m^2 IV; day 29 cyclophosphamide 1000 mg/m^2 IV; days 29-32,36-39 cytarabine 75 mg/m^2 IV or SC; days 29-42 6-thioguanine 60 mg/m^2 orally daily; days 1,29,36 methotrexate 15 mg intrathecal

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