Leveraging Model-Informed Bioequivalence and Non-Inferiority Analyses to Waive the Need for a Phase-III Efficacy Study of Hamsyl® in Paediatric Acute Lymphoblastic Leukaemia

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INTRODUCTION

- **Asparaginase in Treating Acute Lymphoblastic Leukaemia (ALL):**
  - **ALL** is the most common cancer in children younger than 15 years [1] and depends on extracellular asparagine for growth.
  - **L-asparaginase** is essential in multi-agent chemotherapy for paediatric ALL.
  - **Pegaspargase,** a pegylated form of L-asparaginase, has lower immunogenicity and hypersensitivity compared to native L-asparaginase.
  - **Oncaspar®** was the first US-FDA approved pegaspargase, but its high cost and limited availability constrained access in low- and middle-income countries [2].
  - **Hamsyl®** was approved in India as a more affordable biosimilar to improve access.

- **Pharmacokinetics (PK) Bioequivalence (BE) Study to Compare Hamsyl® with Oncaspar®** [3]:
  - **BE analysis** was performed on **21** (10 Hamsyl®, 11 Oncaspar®) **paediatric relapsed ALL patients** after a single intramuscular dose of 1000 IU/m².
  - **BE was concluded** based on AUC_{0-t}: GMR = 95.05% (90% CI: 75.07%–120.33%), falling within the predefined BE range (75%–133%).
  - **Pharmacodynamics, immunogenicity, and safety profiles** were also **comparable** between the products.

OBJECTIVE

To use **modelling and simulations** to strengthen the available evidence and confirm the **bioequivalence and non-inferiority** of **Hamsyl®** versus the reference Oncaspar® in paediatric patients with ALL.

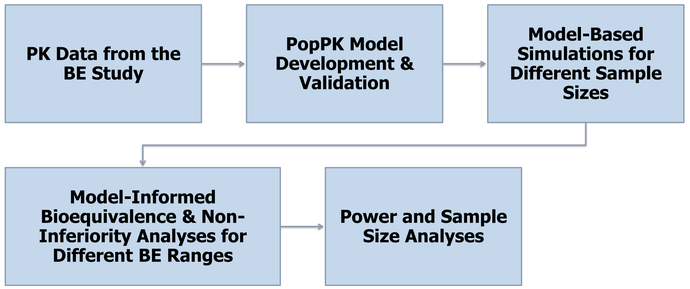
METHODOLOGY

Table 1 – Summary of Baseline Characteristics in the Analysis Population
(Median [Min - Max])

	Hamsyl® (N=10)	Oncaspar® (N=11)	Total (N=21)
Age (yrs)	11 [6, 15]	8 [6, 14]	9 [6, 15]
Weight (kg)	29.2 [14, 46.5]	24,5 [10, 43]	27.5 [10, 46.5]
BSA (m²)	1.02 [0.65, 1.46]	0.95 [0.72, 1.35]	1 [0.65, 1.46]

BSA: body surface area; Max: maximum; Min: minimum.

Figure 1 – Modelling and Simulations Approach Used



BE: bioequivalence; PK: pharmacokinetics; PopPK: population pharmacokinetics.
Simulations were conducted at the recommended dose of 2500 IU/m², supported by evidence that Oncaspar® exhibits dose-proportional pharmacokinetics.

CONTACT

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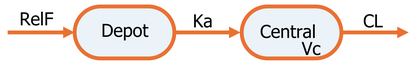
RESULTS

PopPK Modeling:

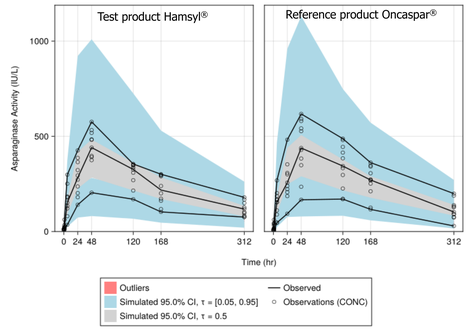
- A **one-compartment** model with **first-order absorption and linear elimination**, incorporating **BSA effect** on clearance (CL) and volume of distribution (Vc) best described the PK data.
- **CL** and **Vc** were estimated at **0.010 L/hr** and **0.193 L**, respectively.
- The **relative bioavailability** of Hamsyl® compared to Oncaspar® was estimated to be **0.974**.

Figure 2 – Schematic of the Final PopPK Model



CL: clearance; Ka: first-order absorption rate; RelF: relative bioavailability; Vc: volume of distribution.

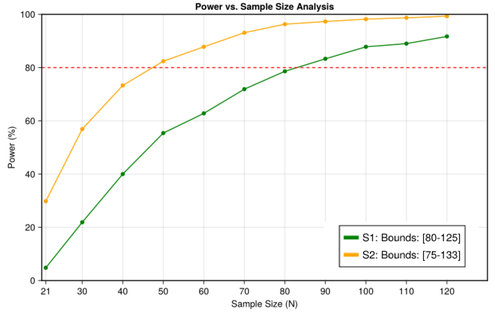
Figure 3 – Visual Predictive Check of the Final PopPK Model



Model-Informed Bioequivalence (MIBE) Analysis:

Approximately 80 subjects are required to achieve at least 80% power considering standard BE range of 80%-125% [4].

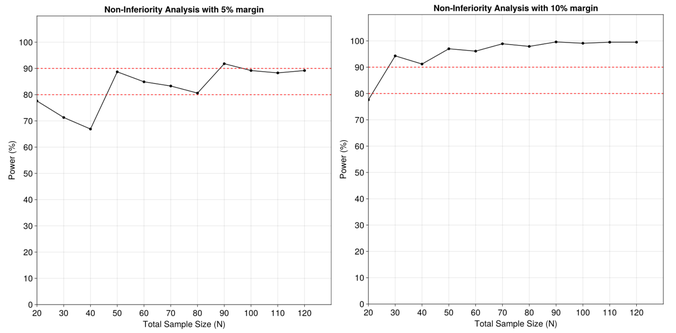
Figure 4 – Power versus Sample Size From MIBE Analysis



Model-informed Non-Inferiority (MINI) Analysis:

NI error margins (−5% to −10%) could achieve ≥80% power with fewer than 50 subjects.

Figure 5 – Power versus Sample Size From MINI Analysis



NI criterion: percentage of subjects achieving target nadir serum asparaginase activity ≥ 100 IU/L at the end of Day 14

CONCLUSIONS

- These integrated analyses demonstrate that **Hamsyl® is bioequivalent to Oncaspar®** with a stringent BE acceptance range of 80%-125%.
- Moreover, **Hamsyl® is non-inferior to Oncaspar®** in terms of nadir serum asparaginase activity.

→ These findings **obviate the need for a traditional Phase III efficacy study**.

REFERENCES

[1] Childhood Leukemia Cancer Stat Facts [Internet].
[2] Oncaspar® (pegaspargase) injection, prescribing information. Servier Pharmaceuticals LLC [Internet]. 2024.
[3] Nookala Krishnamurthy M, Narula G, Gandhi K, Awase A, Pandit R, Raut S, et al. Randomized, Parallel Group, Open-Label Bioequivalence Trial of Intramuscular Pegaspargase in Patients With Relapsed Acute Lymphoblastic Leukemia. JCO Glob Oncol. 2020;6:1009–16.
[4] Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application [Internet]. 2021.