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Establishing Bioequivalence of GBL19, a Recombinant Asparaginase Biosimilar, Through PopPK Modeling and Virtual Bioequivalence Analysis

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Introduction

- **Acute Lymphoblastic Leukaemia (ALL)** is a hematologic malignancy and the **most common cancer in children**.
- It accounts for **~30% of all paediatric cancers** and **~80% of childhood leukaemia cases**.
- ALL cells depend on **asparagine** for survival; depletion leads to **leukaemic cell death**.
- **Asparaginase (ASNase),** and enzyme converts **L-asparagine into aspartic acid, and ammonia**, thereby reducing circulating asparagine.
- Normal cells **synthesize asparagine**, so they are less affected by ASNase treatment.
- **Spectrila®** is the **first recombinant E.Coli derived ASNase** approved by **EMA (2016)**.
- **Gennova Pharmaceuticals Limited** has developed a **cost-effective biosimilar version of Spectrila®**, intended for use in paediatric ALL therapy.

Key Challenges

- It is **not ethical** to perform **standard BE trials** (with intense PK sampling) in **paediatric patients**.
- **Only adult healthy volunteer PK data** is **available** for both formulations.

Aim & Objective

Aim

- To demonstrate the **bioequivalence and efficacy of the Test drug in the paediatric population through extrapolation of adult BE data**, thereby supporting a **Phase III trial waiver** without the need for paediatric efficacy studies.

Objective

- This objective of this study was to demonstrate the **non-inferiority of GBL19 compared to Spectrila®** using population pharmacokinetic (PopPK) and model based bioequivalence (MBBE) analysis .

Methodology

Bioequivalence study in healthy adult subjects (Spectrila® vs GBL19)

Perform NCA and Bioequivalence analysis (AUC and Cmax)

Develop PopPK model from the BE study data

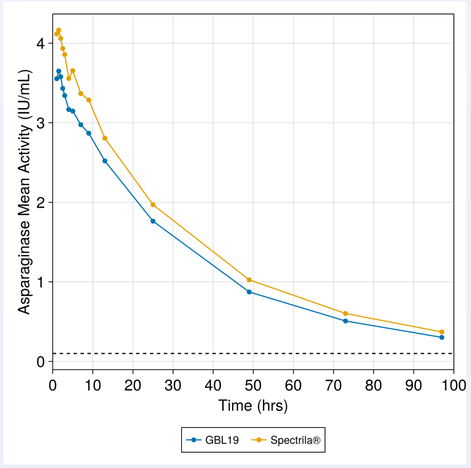
Scale PopPK parameters to paediatric population

Virtual bioequivalence analysis

Non-inferiority analysis

Results

Fig 1: Time vs Concentration Plot

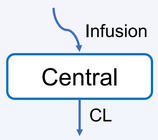


Results (Contd.)

- Bioequivalence analysis was conducted to assess the **AUC** and **Cmax** of the test and reference products. The results demonstrated that both parameters fell **within the FDA's acceptable range of 80% - 125%**, confirming that the test product passed the bioequivalence criteria.
- A **one-compartment model with zero order absorption** was developed.

$$CLi = tvcl * \frac{Wt}{60.75}^{0.51} * 1.23^{\text{Gender}} * \exp(\eta cl)$$

$$Vci = tvvc * \frac{Wt}{60.75}^{0.52} * 1.18^{\text{Gender}} * \exp(\eta vc)$$



where

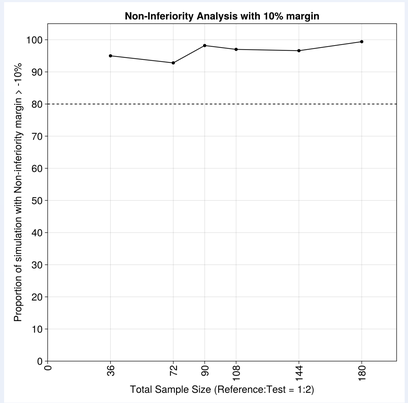
$tvcl$ – typical clearance (L/hr),

$tvvc$ – typical volume of distribution for central compartment (L).

Table 1: Final Model Estimates

Parameter	Description (Units)	Final Estimate	RSE (%)	Bootstrap 95% CI
tvcl	Clearance (mL/hr)	48.65	2.9	[45.91 - 51.28]
tvvc	Volume of distribution (mL)	1808.48	2.75	[1707.04 - 1901.41]
θrelbio	Relative Bioavailability	0.86	3.22	[0.8 - 0.91]
θwtoncl	Weight on CL	0.51	35.4	[0.13 - 0.82]
θwtonvc	Weight on Vc	0.52	32	[0.2 - 0.84]
θgendercl	Gender on CL	1.23	3.38	[1.16 - 1.32]
θgendervc	Gender on Vc	1.18	3.32	[1.11 - 1.26]
Ω_BSV CL	IIV on CL (CV%)	13.8	19.63	[0.01 - 0.03]
Ω_BSV Vc	IIV on Vc (CV%)	14.08	19.7	[0.01 - 0.03]
σ_add	Additive error (IU/mL)	0.07	18.68	[0.05 - 0.1]
σ_pro	Proportional error (CV%)	0.08	11.19	[0.06 - 0.1]

Fig 2: Non-Inferiority Analysis



The non-inferiority margin was set at 5% and 10%. In the total sample sizes of 88 & 72, the difference between the probabilities of simulation with non-inferiority margins of > -5% and > -10% was greater than 80% & 90%, respectively.

Conclusion

- Adult bioequivalence trial data was **well characterized by the PopPK model**.
- **GBL-19** was **non-inferior to Spectrilla** for the given efficacy endpoint even at small sample sizes.
- The non-inferiority results look better with the 10% margin of error specially at the lower sample sizes as it is a more relaxed criteria
- Phase 3 trial with sample size of ~ 100 (88 for 1:1 and 87 for 2:1) is adequately powered for the non-inferiority analysis with 5 and 10% error margins.

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Acknowledgement

Pumas AI: www.pumas.ai/resources