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Safety, Pharmacokinetics, and Efficacy of Eliglustat Administered With and Without Imiglucerase in Paediatric Participants With Gaucher Disease Type 1 or 3: The ELIKIDS Study

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INTRODUCTION

- Gaucher disease type 1 (GD1) is an autosomal recessive lysosomal storage disorder caused by an inherited deficiency of acid-β-glucosidase. This deficiency results in the progressive accumulation of glucosylceramide (GL-1) and glucosylsphingosine (lyso-GL1) affecting multiple systems and leading to a range of clinical manifestations which include spleen and liver enlargement, anaemia, thrombocytopenia, and bone-related issues[1]
- Gaucher disease type 3 (GD3), the sub-acute or chronic neuronopathic form, presents with visceral and haematological manifestations as well as neurological symptoms[1]
- Eliglustat, a potent and specific glucosylceramide synthase inhibitor, is approved as a first-line oral substrate reduction therapy (SRT) for adults with GD1 who are cytochrome P450 2D6 (CYP2D6) poor, intermediate, or extensive metabolizers, and provides a non-invasive treatment option to bi-monthly intravenous enzyme replacement therapy (ERT) infusions. Both treatment naïve adults with GD1 and adults switching from ERT have shown long term benefit with eliglustat treatment. In most adult patients, efficacy of eliglustat appears comparable to ERT, and the safety profile has been shown to be acceptable
- Currently, ERT is the standard of care for paediatric patients with GD; SRT is not approved for use in children
- ELIKIDS (NCT03485677) is an ongoing multicentre, open-label trial with 2 cohorts (eliglustat alone and eliglustat in combination with imiglucerase) in paediatric participants aged 2 to <18 years of age with GD1 and GD3

Clinical Presentation of Gaucher Disease in Pediatric Population

Children or adolescents with GD1 often have marked hepato- and splenomegaly, easy bruising/bleeding/hypermenorrhagia and slower than normal growth and pubertal development

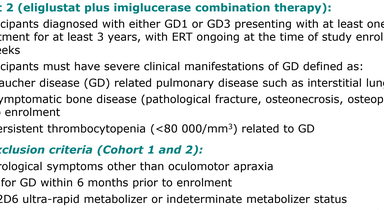
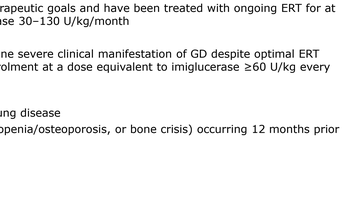


Figure adapted with permission from Kaplan P, et al. *Arch Pediatr Adolesc Med* 2006; 160:603.

Treatment Approaches to Gaucher Disease[1]



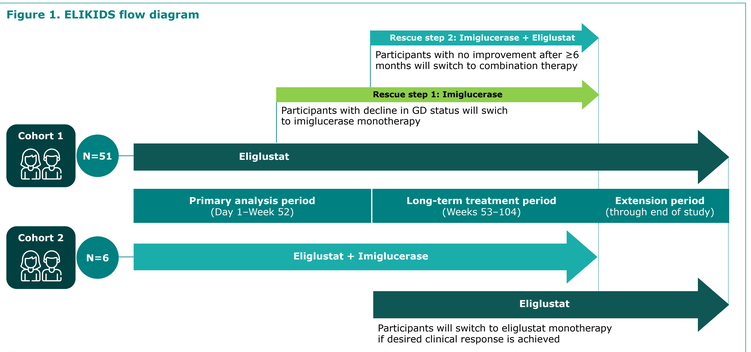
OBJECTIVES

- **Primary objectives**: To evaluate safety and pharmacokinetics (PK) of eliglustat in paediatric participants
- **Secondary objectives**: To evaluate the efficacy of eliglustat and impact on quality of life in paediatric participants

STUDY DESIGN

- The study comprises a primary analysis treatment period (PAP; Day 1 to Week 52), a long-term treatment period (Week 53 to 104), and an extension period (through end of study) for participants who continue to demonstrate clinical benefit from eliglustat monotherapy by Week 104 **(Figure 1)**
- Eliglustat is dosed according to the participant's predicted CYP2D6 metabolizer status and based on age and weight category
- The present study reports the interim analysis results for safety across all phases with a data cut-off date of 21 June 2023; PK and efficacy endpoints were assessed after participants completed the PAP

Figure 1. ELIKIDS flow diagram



GD, Gaucher disease.

Key inclusion criteria

Cohort 1 (eliglustat monotherapy):

- Participants diagnosed with either GD1 or GD3 who met prespecified therapeutic goals and have been treated with ongoing ERT for at least 2 years at the time of enrollment at a dose equivalent to imiglucerase 30–130 U/kg/month

Cohort 2 (eliglustat plus imiglucerase combination therapy):

- Participants diagnosed with either GD1 or GD3 presenting with at least one severe clinical manifestation of GD despite optimal ERT treatment for at least 3 years, with ERT ongoing at the time of study enrolment at a dose equivalent to imiglucerase ≥60 U/kg every 2 weeks
- Participants must have severe clinical manifestations of GD defined as:
  - Gaucher disease (GD) related pulmonary disease such as interstitial lung disease
  - Symptomatic bone disease (pathological fracture, osteonecrosis, osteopenia/osteoporosis, or bone crisis) occurring 12 months prior to enrolment
  - Persistent thrombocytopenia (<80 000/mm^3) related to GD

Key exclusion criteria (Cohort 1 and 2):

- Neurological symptoms other than oculomotor apraxia
- SRT for GD within 6 months prior to enrolment
- CYP2D6 ultra-rapid metabolizer or indeterminate metabolizer status
- Partial or total splenectomy if performed within 2 years prior to enrolment

RESULTS

Baseline characteristics

- From June 2018 to July 2022, a total of 57 participants were enrolled across 21 sites in 10 countries, 51 participants in Cohort 1 and 6 participants in Cohort 2 (n=3, GD-related pulmonary disease; n=3, symptomatic bone disease; **Table 1**)
- The mean age of the participants was 12 years (range 3 to 17) with a greater number of participants (36 [63.2%]) in the 12 to <18-year age group
- Overall, most participants enrolled in the study have GD1 (86%), are CYP2D6 extensive metabolizers (96%), and were assigned to Cohort 1 (89%)
- All participants in Cohort 2 had haematological and visceral parameters within the prespecified therapeutic goals similar to Cohort 1

Table 1. ELIKIDS baseline characteristics

		Cohort 1 (N=51)	Cohort 2 (N=6)
GD type, n (%)	GD1	46 (90)	3 (50)
	GD3	5 (10)	3 (50)
Age at diagnosis, years		4.9 ± 3.3	2.3 ± 2.8
Age at enrolment, years		12.2 ± 3.4	10.2 ± 4.5
ERT prior to enrolment, years		7.2 ± 3.8	4.9 ± 1.2
Female, n (%)		26 (51)	2 (33)
White race, n (%)		45 (88)	5 (83)
CYP2D6 EM status, n (%)		49 (96)	6 (100)
N370S variant present, n (%)		36 (71)	1 (17)
Spleen volume, MN		3.4 ± 1.5	3.7 ± 1.4
Liver volume, MN		1.0 ± 0.2	1.1 ± 0.3
Platelet count, x10^9/L		214 ± 51	252 ± 76
Haemoglobin, g/L		131 ± 26	134 ± 15
Glucosylsphingosine, ng/mL		39.1 ± 1.9	38.7 ± 9.6
Chitotriosidase, nmol/h/mL		1406 ± 2020	2173 ± 3183
Total body BMD Z-score		−2.6 ± 1.8	−4.6 ± 3.1
Total body BMB score		9.2 ± 2.2	8.7 ± 1.6

Data are mean ± SD for continuous type, unless otherwise stated.
BMB, bone mineral burden; BMD, bone mineral density; CYP2D6, cytochrome P450 2D6; EM, extensive metabolizer; ERT enzyme replacement therapy; GD, Gaucher disease; GD1, Gaucher disease type 1; GD3, Gaucher disease type 3; MN multiples of normal; SD standard deviation.

Safety and PK outcomes

- A total of 53 (93%) enrolled participants experienced ≥1 treatment-emergent adverse event (TEAE) with no meaningful difference by age group, gender, or GD type
- The incidence of TEAEs reported in >5% of participants in the safety population by system organ class (SOC) and preferred term (PT) during the study are listed in **Table 2**
- The most frequently reported adverse drug reaction (ADR) was dyspepsia (11%); splenomegaly, headache, fatigue, and dry skin were the only other ADRs reported in >1 participant
- No participants experienced permanent treatment discontinuation due to a TEAE
- No deaths were reported
- No new adverse reactions were reported with eliglustat use

Table 2. TEAEs occurring in >5% of participants in either treatment group regardless of relationship to study drug

Adverse events n (%)	Cohort 1 (N-51)	Cohort 2 (N=6)	All participants (N=57)
Nasopharyngitis	12 (23.5)	2 (33.3)	14 (24.6)
COVID-19	11 (21.6)	2 (33.3)	13 (22.8)
Headache	7 (13.7)	1 (16.7)	8 (14.0)
Dyspepsia	7 (13.7)	1 (16.7)	8 (14.0)
Arthralgia	7 (13.7)	1 (16.7)	8 (14.0)
Vomiting	6 (11.8)	2 (33.3)	8 (14.0)
Pharyngitis	6 (11.8)	0	6 (10.5)
Splenomegaly	5 (9.8)	0	5 (8.8)
Vitamin D deficiency	5 (9.8)	0	5 (8.8)
Nausea	4 (7.8)	1 (16.7)	5 (8.8)
Pyrexia	4 (7.8)	1 (16.7)	5 (8.8)
Fall	4 (7.8)	0	4 (7.0)
Abdominal pain	3 (5.9)	1 (16.7)	4 (7.0)
Epistaxis	3 (5.9)	1 (16.7)	4 (7.0)
Upper respiratory tract infection	3 (5.9)	0	3 (5.3)
Iron deficiency anaemia	3 (5.9)	0	3 (5.3)
Constipation	3 (5.9)	0	3 (5.3)
Dry skin	3 (5.9)	0	3 (5.3)
Pain in extremity	3 (5.9)	2 (33.3)	5 (8.8)
Dysmenorrhoea	3 (5.9)	0	3 (5.3)
Cough	2 (3.9)	1 (16.7)	3 (5.3)
Diarrhoea	2 (3.9)	2 (33.3)	4 (7.0)
Abdominal pain upper	2 (3.9)	1 (16.7)	3 (5.3)
Bone pain	2 (3.9)	1 (16.7)	3 (5.3)
Groin pain	2 (3.9)	1 (16.7)	3 (5.3)
Fatigue	2 (3.9)	1 (16.7)	3 (5.3)
Ligament sprain	2 (3.9)	1 (16.7)	3 (5.3)

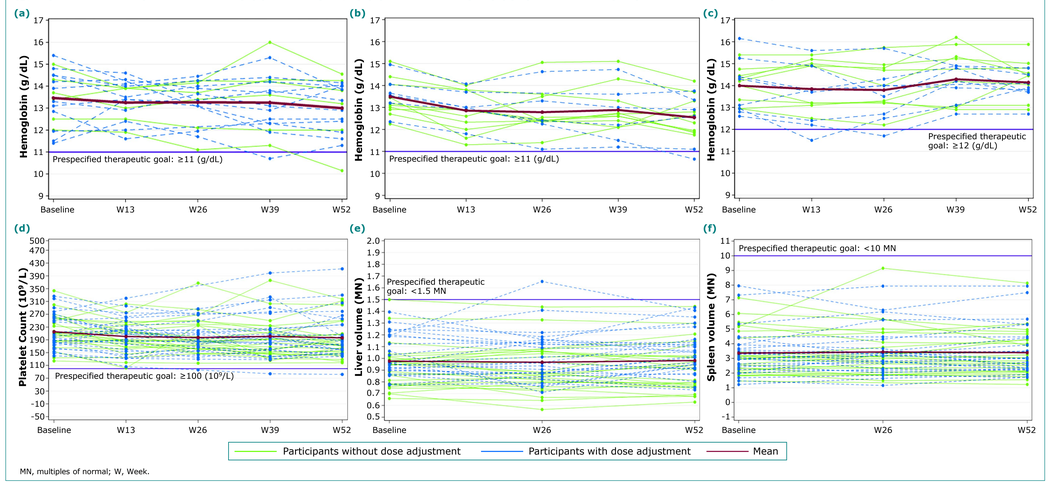
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

- The safety profile of eliglustat observed in paediatric participants with GD1 and GD3 is in line with the established safety profile seen in adults with GD1 and as anticipated for the paediatric population
- No changes in the immunogenicity profile of imiglucerase were observed in participants who switched to imiglucerase treatment
- The PK exposure in the paediatric participants administered the revised dosing regimen during the PAP was generally within the target exposure in corresponding adult participants in Phase 2 and 3 eliglustat clinical trials using a dose regimen based on CYP2D6 phenotype metabolizer status and weight
- The target mean (5th–95th percentile) exposure for the study based on the adult physiologically based pharmacokinetic modelling (PBPK) modelling prediction is C_{max} (ng/mL): 27.0 (8.61–60.5) and $AUC_{0-\tau}$ (h*ng/mL): 190 (51.1–402)
- The mean±SD values for C_{max} (ng/mL) and $AUC_{0-\tau}$ (h*ng/mL) at Week 52 in paediatric participants were 34.6±34.7 and 179±190, respectively

Efficacy outcomes

- During the PAP, the majority of participants receiving eliglustat monotherapy (Cohort 1) successfully maintained their haemoglobin levels (96%), platelet counts (98%), and liver and spleen volumes (100%) within the prespecified therapeutic goals set for study entry **(Figure 2)**

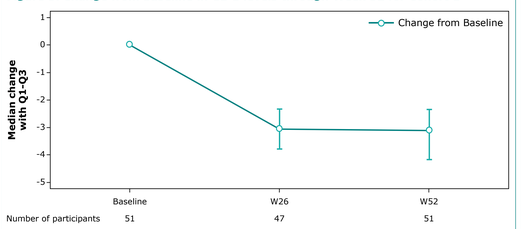
Figure 2. Individual participants line graph of (a) haemoglobin (g/dL) for 2 to <12 years old (b) haemoglobin (g/dL) for 12 to <18 years old females (c) haemoglobin (g/dL) for 12 to <18 years old males (d) platelets (10^9/L) (e) liver volume (MN) (f) spleen volume (MN) in Cohort 1- Full analysis set



MN, multiples of normal; W, Week.

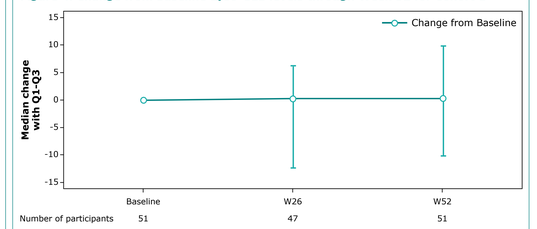
- There was an improvement or maintenance in bone mineral density Z-scores and bone mineral burden scores
- The median GL-1 level decreased throughout the PAP consistent with the mechanism of action of eliglustat and the median lyso-GL1 level remained relatively stable **(Figure 3 and 4)**
- Ninety-two percent (47/51) of participants remained on eliglustat monotherapy throughout the PAP; 4 participants switched to imiglucerase due to declining GD-related clinical parameters
- All participants receiving eliglustat plus imiglucerase combination therapy (Cohort 2) completed the PAP on eliglustat plus imiglucerase combination therapy

Figure 3. Change from baseline in GL-1 levels through Week 52 for Cohort 1



GL-1, glucosylceramide; Q1, first quartile; Q3, third quartile; W, Week.

Figure 4. Change from baseline Lyso-GL1 levels through Week 52 for Cohort 1



lyso-GL-1, glucosylsphingosine; Q1, first quartile; Q3, third quartile; W, Week.

CONCLUSIONS

- Eliglustat was found to be well tolerated in paediatric participants with GD1 and GD3 and no new safety issues were identified throughout the reporting period
- PK exposure is aligned with the target exposure seen in the adult eliglustat clinical trials
- Majority of study participants, whether on eliglustat monotherapy or combination therapy with imiglucerase maintained Gaucher-related clinical parameters within prespecified therapeutic goals during PAP

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ACKNOWLEDGMENTS
Medical writing support for this poster was provided by Parag Betkar from Sanofi.
DISCLOSURES
Pilar Giraldo: has been involved in premarketing studies with Genzyme, Protalix and Idorsia, and has received grants from Sanofi-Genzyme and Takeda
Guillermo I Drelichman and **Binfeng Xia:** have nothing to disclose
Gulden Gokçay: has received consultancy and travel grants from Sanofi-Genzyme, Takeda, Biomarin and Nutricia
Isabela Batsu, **Julie Kissell**, **Dmitry Cherkasov**, **Ning Li**, **Sefika Uslu Cil**: are employees of Sanofi and may hold shares and/or stock options in the company

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FUNDING
The study was funded by Sanofi.

If you have questions about this poster, please email giraldocastellano@gmail.com and julie.kissell@sanofi.com.

e-Poster presented at European Hematology Association Hybrid Congress 2024 – Madrid, Spain, June 13–16, 2024