17 November 2025
EMA/OD/0000242073
EMADOC-1700519818-2329115
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Aqneursa (acetylleucine)
Treatment of Niemann-Pick disease
EU/3/17/1848

Sponsor: Intrabio Ireland Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Designated active substance(s)	Acetylleucine
Other name(s)	-
International Non-Proprietary Name	Acetylleucine
Tradename	Aqneursa
Orphan condition	Treatment of Niemann-Pick disease
Sponsor's details:	Intrabio Ireland Limited 10 Earlsfort Terrace Dublin 2 Co. Dublin D02 T380 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Intrabio Ltd
COMP opinion	16 February 2017
EC decision	20 March 2017
EC registration number	EU/3/17/1848
Post-designation procedural history	
Transfer of sponsorship	Transfer from Intrabio Ltd to Intrabio Ireland Limited – EC decision of 10 April 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Frantisek Drafi
Applicant	Intrabio Ireland Limited
Application submission	3 June 2024
Procedure start	20 June 2024
Procedure number	EMA/H/C/006327/0000
Invented name	Aqneursa
Therapeutic indication	Aqneursa is indicated for the treatment of neurological manifestations of Niemann-Pick type C (NPC) disease, in combination with miglustat, or as a monotherapy in patients where miglustat is not tolerated, in adults and children aged 6 years and older and weighing at least 20 kg. Further information on Aqneursa can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/aqneursa
CHMP opinion	24 July 2025
Re-examination of CHMP opinion	13 November 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Joao Rocha
Sponsor's report submission	20 December 2024
COMP discussion	10-12 June 2025
COMP opinion (adoption via written procedure)	25 July 2025
Re-examination of COMP opinion (adoption via written procedure)	17 November 2025

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on preclinical and preliminary clinical data showing improvement of ataxia symptoms;
- the condition is chronically debilitating and life-threatening in particular due to complications such as neurological degeneration, splenomegaly, and hepatomegaly. The majority of patients with Niemann-Pick disease type A die before two years of age, while patients with other forms usually die in their twenties;
- the condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing acetylleucine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement of ataxia symptoms in patients affected by Niemann-Pick disease who were not adequately controlled with the currently authorized treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing acetylleucine as an orphan medicinal product for the orphan indication: treatment of Niemann-Pick disease".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Niemann-Pick Disease (NPD) comprises a group of autosomal-recessive inherited lysosomal storage disorders. These disorders have in common the deficient and/or very low activity of the lysosomal hydrolase, acid sphingomyelinase. Two disease subgroups are described in the literature, the first one is characterized by a deficiency of acid sphingomyelinase ("types A & B", caused by mutations in the SMPD1 gene), and the second is due to defective function in cholesterol transport ("type C", caused by mutations in the NPC1 and NPC2 genes). Type A is characterized by early hepatosplenomegaly and profound CNS manifestations, while type B only rarely exhibit CNS manifestations. Type C patients also manifest organomegaly and neurodegeneration (Patterson and Walkley, Mol Genet Metab. 2017 Jan - Feb).

The target patient population of the current application is Niemann-Pick disease, type C (NPC). NPC exhibits phenotypic heterogeneity, comprising systemic, neurological, and psychiatric features. Neonatal NPC patients frequently have an increase in bile acid concentration in the liver, and 10% of these patients die of liver failure before six months of age. The symptoms of NPC patients who survive infancy are dominated by progressive neurodegeneration, characterized by features such as cerebellar ataxia, vertical supranuclear gaze palsy, dysphagia, gait disorder with falls and dementia.

The approved therapeutic indication "*Aqneursa is indicated for the treatment of neurological manifestations of Niemann-Pick type C (NPC) disease, in combination with miglustat, or as a monotherapy in patients where miglustat is not tolerated, in adults and children aged 6 years and older and weighing at least 20 kg*" falls within the scope of the designated orphan condition "treatment of Niemann-Pick disease".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition is considered life-threatening and chronically debilitating due to progressive neurological diseases, such as epileptic seizures, ataxia, dystonia/dysmetria, dysarthria, dysphagia and gelastic cataplexy. The majority of patients die between 10 and 25 years of age, patients with early-onset disease usually die before the age of 5 years. Besides progressive neurological disease, the common cause of death is bronchopneumonia, most likely due to repeated aspiration following progressive dysphagia.

Number of people affected or at risk

At the time of orphan designation, the estimated prevalence for the condition was 1 per 100,000 (0.1 per 10,000), a figure significantly below threshold for Orphan Designation of 5 affected persons per 10,000 in the European Union.

A PubMed search was conducted using the search terms prevalence and Niemann-Pick Type C for the intervening period from 2017 till present. No new reports published since 2017 of original research on the prevalence of NPC in Europe were retrieved.

The following reports have been published which support this estimated prevalence:

- Patterson 2020 reported a prevalence of 1 per/ 150,000 (=0.67 per 100,000) in Western Europe.
- Burton et al 2021 surveyed a database of 308 million individuals and estimated a prevalence of up to 0.29 per 100,000 in the US. The authors highlighted the heterogeneous and nonspecific clinical presentation that is a key challenge in recognizing NPC, so that many individuals with NPC may be misdiagnosed or undiagnosed.

Since the orphan condition also entails Niemann-Pick disease (NPD) types A and B, the prevalence calculation is amended to add the prevalence value for these two disease types, as discussed in the Orphan Maintenance Assessment Report for Xenpozyme (olipudase alfa) in 2022. Combining one of the highest reported birth prevalence values from Portugal of 0.06 per 10,000 (Pinto et al., 2004) with a disease duration of 65 years, based on the data described by McGovern and colleagues (McGovern et al., Genet Med. 2013) and the surviving population ages described by Hollak (Hollak et al., Mol Gen Metab. 2012), the resulting prevalence estimate for NPD types A and B is 0.037 per 10,000.

Considering the above, the COMP accepted a combined prevalence estimate of approximately 0.14 in 10,000 persons in the European Union for the overarching condition of Niemann-Pick disease.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Miglustat is the only medicine authorised for NPC in the European Union/European Economic Area. Miglustat is considered "standard of care" therapy per the International Consensus Clinical Management Guidelines for NPC [Geberhiwot et al. 2018]. *Zavesca (miglustat) is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (see sections 4.4, and 5.1).*

Miglustat is considered a satisfactory method NPC patients and a discussion on significant benefit will be needed.

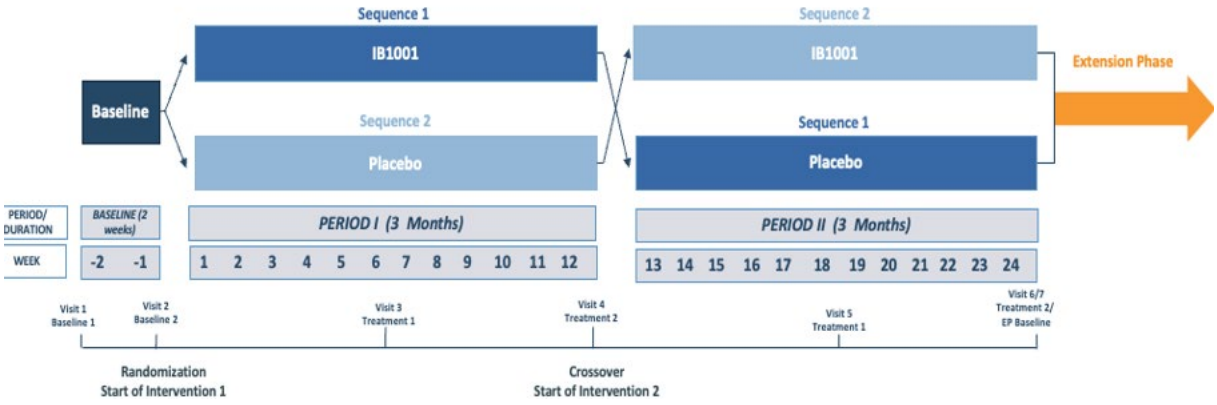
Significant benefit

The sponsor argues that Aqneursa (levacetylleucine) represents a clinically relevant advantage in the treatment of NPC patients, based on the pivotal study results.

The efficacy and safety of levacetylleucine for treatment of NPC was studied in one pivotal randomised, double-blind, placebo-controlled, 2-period crossover study in a total of 60 patients. Patients were randomised in a 1:1 ratio to receive either levacetylleucine or placebo for 12 weeks in Period I. In

Period II, patients switched to the opposite (either levacetylleucine or placebo) for 12 weeks. Patients aged ≥ 13 years received 4 g/day. The levacetylleucine dose in children under 13 years was based on patient's body weight. Of the 60 randomised patients (37 adults and 23 paediatric patients). The median age at treatment initiation was 25 years (range: 5 to 67 years). To be eligible for the study, patients had to have a baseline SARA score of 7 to 34 points (2-7 range of the gait subtest of SARA, able to perform 9Hole Peg test with dominant test). Therefore, the efficacy and safety in patients without neurological symptoms and very severe patients have not been studied. The majority of patients (51/60 or 85%) received concomitant treatment with miglustat during the study.

Figure 1. Pivotal study design (Aqneursa/levacetylleucine for NPC)



The pivotal study met its primary endpoint as measured by the SARA, a valid measure of neurological signs and symptoms in lysosomal storage disorders with central nervous system involvement (such as NPC) (Table 1). A 1-point change represents a clinically meaningful and is a transition reflecting the gain or loss of complex function [Park et al. 2024]. Patients receiving placebo in Period I of the crossover study had no meaningful change in the mean SARA score compared to those patients on levacetylleucine, who had a substantial change. Further, patients who received levacetylleucine in Treatment Period I followed by placebo in Treatment Period II experienced significant worsening of symptoms on placebo, which effectively served as a washout from levacetylleucine, reflecting a deterioration neurological signs and symptoms when treatment with levacetylleucine was stopped (see Table 1).

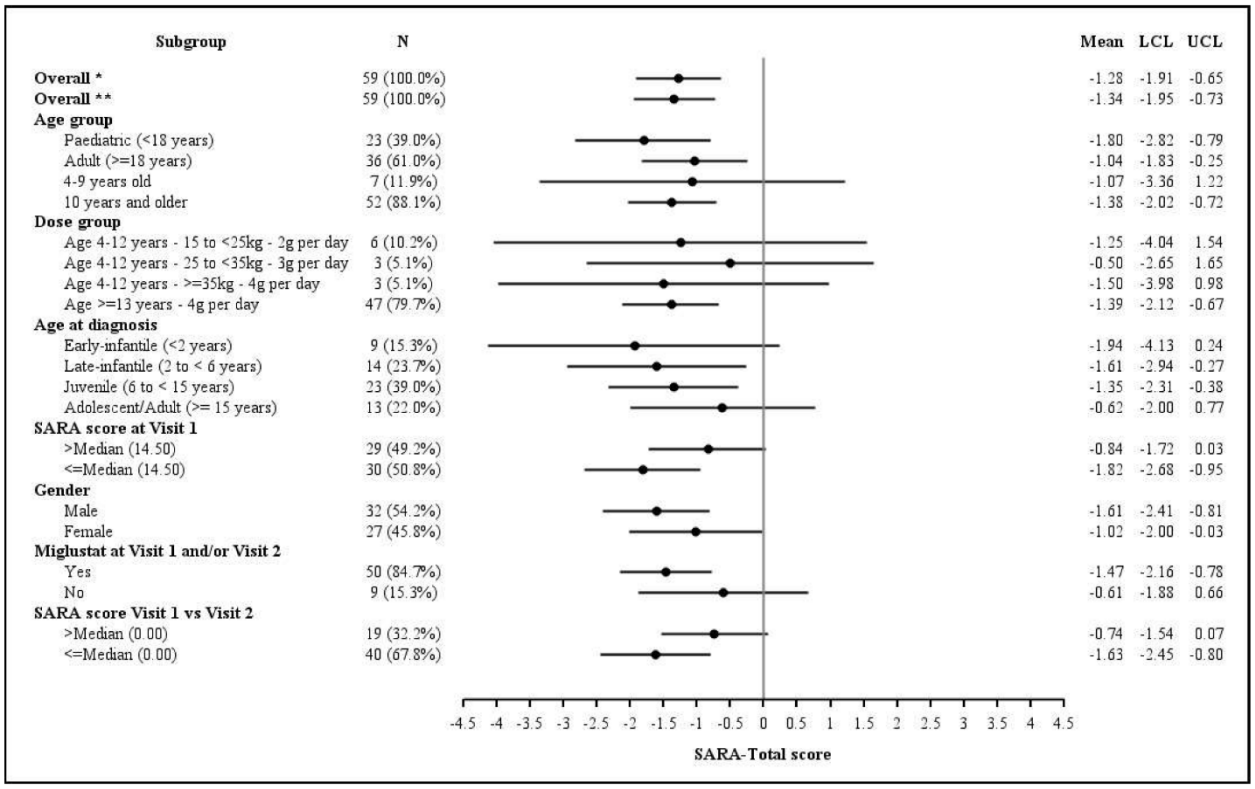
Table 1. Summary of scale for the assessment and rating of ataxia (SARA) efficacy results*

Effect/Variable	**Mean difference (SD)**	**Estimate (SE)**	**95% CI**	**p-value****
Baseline value	--	0.95 (0.04)	(0.86, 1.04)	< 0.001
Treatment effect (levacetylleucine versus placebo)	--	-1.28 (0.31)	(-1.91, -0.65)	< 0.001
Levacetylleucine total change versus baseline	- 1.97 (2.43)	--	--	--
Placebo total change versus baseline	-0.60 (2.39)	--	--	--

CI = confidence interval; SD = standard deviation; SE = standard error.
* The change from baseline was assessed at the end of Period 1 (Week 12) and the end of Period 2 (Week 24).
** Two-sided p-value.

A forest plot for the SARA total score of the differences (between IB1001 and placebo) with 95% CIs of all subgroups of the ITT population is presented in Figure 2. For all subgroups, a negative estimator for SARA total score difference (i.e., improvement) was observed, demonstrating consistent improvement with levacetylleucine compared to placebo that was observed across all patient subgroups on the SARA endpoint (including age (which included a broad age range, 5 to 67 years), age of disease onset, disease severity, and miglustat use). The COMP took particular note of the efficacy analysis in the patient subset receiving levacetylleucine in combination with miglustat (i.e. 85% of the patient population in the pivotal study). Levacetylleucine in combination with miglustat achieved a significantly higher reduction in the "Scale for the Assessment and Rating of Ataxia" (SARA) total score (primary efficacy endpoint), as compared to the placebo group which only received background treatment with miglustat. A lower SARA total score indicates clinical improvement. The SARA scale ranges from 0 to 40, with 0 indicating no ataxia and 40 indicating the most severe ataxia.

Figure 2. Forest Plot SARA Total Score at Visit 4 or 6 with 95% Confidence Intervals



The pivotal study also met its secondary mDRS, SCAFI, and CGI-I endpoints and exploratory mSARA and axial SARA endpoints, showing consistent improvement across efficacy endpoints.

In conclusion, when used in combination with miglustat, Aqneursa has demonstrated to be more efficacious compared to miglustat alone. Furthermore, Aqneursa as monotherapy is also indicated for use in patients where miglustat is not tolerated. The Committee considered that this constitutes a clinically relevant advantage.

4. COMP position adopted on 17 November 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of Niemann-Pick disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.14 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to severe neurological decline and chronically debilitating due to neurological degeneration, splenomegaly, and hepatomegaly;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Aqneursa is of significant benefit to those affected by the orphan condition is considered established. When used in combination with miglustat, Aqneursa has demonstrated to be more efficacious as compared to miglustat alone. Furthermore, Aqneursa as monotherapy is also indicated for use in patients where miglustat is not tolerated. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Aqneursa, acetylleucine for treatment of Niemann-Pick disease (EU/3/17/1848) is not removed from the Community Register of Orphan Medicinal Products.