26 June 2026
EMA/OD/0000288100
EMADOC-1700519818-3297478
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Daybu (trofinetide)
Treatment of Rett syndrome
EU/3/15/1534

Sponsor: Acadia Pharmaceuticals (Netherlands) B.V.

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)	Glycyl-L-2-methylprolyl-L-glutamic acid
Other name(s)	--
International Non-Proprietary Name	Trofinetide
Tradename	Daybu
Orphan condition	Treatment of Rett syndrome
Sponsor's details:	Acadia Pharmaceuticals (Netherlands) B.V. Strawinskylaan 3051 1077 ZX Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	QRC Consultants Ltd.
COMP opinion	16 July 2015
EC decision	10 August 2015
EC registration number	EU/3/15/1534
Post-designation procedural history	
Transfer of sponsorship	Transfer from QRC Consultants Ltd to DLRC Pharma Services Ltd – EC decision of 12 February 2019
Transfer of sponsorship	Transfer from DLRC Pharma Services Ltd to Voisin Consulting Life Sciences – EC decision of 11 December 2023
Transfer of sponsorship	Transfer from Voisin Consulting Life Sciences to Comharsa Life Sciences Limited – EC decision of 29 August 2024
Transfer of sponsorship	Transfer from Comharsa Life Sciences Limited to Acadia Pharmaceuticals (Netherlands) B.V. – EC decision of 19 June 2025
Marketing authorisation	
Rapporteur / Co-rapporteur	Peter Mol / Ewa Balkowiec Iskra
Applicant	Acadia Pharmaceuticals (Netherlands) B.V.
Application submission	20 December 2024
Procedure start	23 January 2025
Procedure number	EMA/H/C/006482
Invented name	Daybu
Proposed therapeutic indication	Daybu is indicated for the treatment of neurobehavioural symptoms of Rett syndrome in adults and paediatric patients aged 5 years and older. Further information on Daybu can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/daybu

CHMP opinion	25 June 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Darius Matusevicius / Ruta Mameniskiene
Sponsor's report submission	13 August 2025
COMP discussion	16-18 June 2026
COMP opinion (adoption via written procedure)	26 June 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2015 was based on the following grounds:

The sponsor Autism Therapeutics Ltd submitted on 25 March 2015 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing glycyl-L-2-methylprolyl-L-glutamic acid for treatment of Rett Syndrome (hereinafter referred to as "the condition"). The sponsor changed to QRC Consultants Ltd. during the evaluation procedure. The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

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 glycyl-L-2-methylprolyl-L-glutamic acid was considered justified based on preliminary clinical data in patients with the condition showing improvement in parameters associated with condition;
- the condition is chronically debilitating and life-threatening particularly due to severe locomotor disability, sleep disturbances, seizures, respiratory complications, development of arrhythmias resulting in decreased life-expectancy;
- the condition was estimated to be affecting approximately 0.5 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.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for 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 glycyl-L-2-methylprolyl-L-glutamic acid as an orphan medicinal product for the orphan indication: treatment of Rett syndrome.

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

Rett syndrome (RTT) is a severe neurodevelopmental disorder characterized by early normal development followed by regression, primarily affecting females. In approximately 96%-98% of patients the condition is monogenic dominant, caused by loss-of-function mutations in the X-linked methyl-CpG-binding protein 2 gene (MECP2), also referred to as "typical" Rett syndrome.

These loss-of-function mutations lead to a cascade of molecular and cellular disturbances characterized by genome-wide transcriptional dysregulation, impaired synaptic plasticity and altered dendritic structure, ultimately compromising neuronal connectivity and communication. In addition, these mutations disturb the balance between excitatory and inhibitory signaling in neural circuits—particularly affecting GABAergic inhibitory neurons—thereby contributing to network instability. Finally, they result in altered expression of key neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), further impairing neuronal development, survival, and synaptic function.

The clinical course of Rett syndrome follows a characteristic staged progression. It begins with an early onset phase in infancy, during which developmental slowing becomes apparent. This is followed by a rapid regression stage, typically occurring between 6 months to 2-3 years of age, marked by the loss of previously acquired skills such as purposeful hand use (at least 30% of individuals remaining without any type of purposeful hand use) and verbal/non-verbal communication as well as emergence of autistic-like behavior, gait abnormalities, seizures and sleep disturbances. Seizures have a lifetime prevalence in RTT of around 90%. Subsequently, patients enter a plateau or pseudo-stationary stage between approximately 2-10 years of age, in which symptoms stabilize and there may be some improvement in social interaction (eye contact) and awareness. Over time, the disease progresses into a late motor deterioration stage usually after 10 years of age into adolescence and adulthood, characterized by a gradual decline in motor function and increasing physical disability, including impairment or inability to walk, scoliosis, and cardiopulmonary complications.

Atypical RTT presents in a minority of patients and encompasses a broader, genetically and phenotypically diverse spectrum of Rett-like conditions, with less stereotyped progression. This subtype may include mutations in MECP2 but also in CDKL5 (early-onset epilepsy phenotype), FOXG1 (congenital variant) or other genes.

The approved therapeutic indication "Daybu is indicated for the treatment of neurobehavioural symptoms of Rett syndrome in adults and paediatric patients aged 5 years and older (see section 5.1)" falls within the scope of the designated orphan condition "Treatment of Rett syndrome".

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

Rett syndrome (RTT) is a severe, progressive neurodevelopmental disorder characterized by a chronically debilitating and life-threatening course. Although affected individuals typically exhibit normal development during the first 6–18 months of life, RTT is marked by early-onset developmental regression, including loss of acquired hand function, language skills, and motor abilities Some of these RTT-specific approaches have been formalised in management guidelines (Baikie et al., 2014; Jefferson et al., 2016; Wandin et al., 2015). This regression results in profound and lifelong disability, with most patients remaining dependent on caregivers for activities of daily living.

RTT involves multisystem dysfunction, affecting neurological, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. Common clinical manifestations include seizures (affecting approximately 90% of patients), autonomic dysfunction (e.g., irregular breathing and cardiac abnormalities), scoliosis, impaired growth, and severe communication deficits. Many of these complications persist throughout life and require continuous monitoring and intervention.

The disorder is associated with increased mortality. Survival rates are reduced, with approximately 50% of patients reaching middle age (Lopes et al., 2024), and reported 5-year mortality rates in adults of around 13% (Halbach et al., 2013). Life-threatening complications primarily arise from respiratory irregularities, cardiac dysfunction, and seizure-related events.

Despite the use of multidisciplinary symptomatic management strategies, no curative treatment exists. Consequently, RTT imposes a substantial long-term burden on both patients and caregivers (Palacios-Ceña et al., 2018; Fu et al., 2020), reinforcing its classification as a chronically debilitating and life-threatening condition.

Number of people affected or at risk

At time of initial orphan designation in 2015 (EU/3/15/1534), the COMP accepted a prevalence estimate of approximately 0.5 in 10,000 persons in the European Union.

For the purpose of orphan maintenance, the prevalence of Rett syndrome (RTT) in Europe was reassessed, based on epidemiologic data up to June 2025. The sponsor now proposes a higher conservative prevalence estimate of approximately 1 in 10,000 persons. A systematic literature search was conducted as well as a review of European registries, particularly the European Rett Syndrome Network and national databases (e.g., SYRENE in France, Italian Rett Database, Barcelona Rett Database). Two complementary estimation methods were applied:

- Direct method: Extraction of reported prevalence data from publications or registries.
- Indirect method: Calculation of prevalence from incidence using the standard epidemiological relationship: Prevalence = Incidence × Disease duration.

Disease duration was approximated by a median survival of 50 years, reflecting the observation that most individuals with RTT survive into adulthood (Tarquinio et al. (2015), Fu et al. (2020), and Lopes et al. (2024)).

Epidemiologic data from literature:

Only one relevant article by Zade and colleagues (2024) provided a direct prevalence rate for the Republic of Ireland. The demographic study, conducted in 2022 using data from the Rett Syndrome Association of Ireland (RSAI), shows a ratio of 1 per 200,000 inhabitants, in the total population in Ireland. This value was considered likely underestimated due to underreporting and registry limitations.

Indirect calculations from European studies yielded low prevalence estimates, of 0.15 and 0.12 per 10,000 respectively, based on cohort-based studies from Poland and Italy (Zade et al., 2024, based on data from Rozensztrauch et al., 2021; Cocca et al., 2019). Additional case reports from multiple European countries - such as Alexandrou et al. (2019) (Cyprus), Henriksen et al. (2018) (Norway), Fuente et al. (2017), Torres et al. (2019) (Spain), and Svedberg et al. (2019) (Sweden) - provided incidence-derived prevalence ranging from 0.003 to 0.60 per 10,000.

Epidemiologic data from European registries

Registry-based data provided more systematic and reliable estimates. Using incidence-derived calculations from registry case counts and Eurostat population data:

- European Rett Syndrome Network (collected since 2008)
  - Croatia: ~0.22 per 10,000
  - Italy: ~0.23 per 10,000
  - Denmark: ~0.32 per 10,000
  - Hungary: ~0.28 per 10,000
  - Romania: ~0.026 per 10,000
  - Spain (Barcelona Rett Database): ~0.26 per 10,000
- SYRENE Registry (France; collected since 2004):
  - ~0.09 per 10,000
- Italian Rett Syndrome Database (collected since 1998):
  - Independently reported estimate 0.7–1 per 10,000 **live born** with RTT.

Based on these registry data, the range of prevalence for Rett Syndrome across the reported countries is from 0.026 per 10,000 in Romania to 0.32 per 10,000 in Denmark.

The sponsor further states that the national **Italian** database reported a prevalence range of 0.7 to 1 per 10,000. However, the COMP pointed out that this value appears not to reflect population prevalence but birth prevalence and should therefore not be considered. This is of particular relevance as the sponsor bases their updated prevalence proposal on the upper end of this **birth prevalence**, i.e. 1 per 10,000 persons.

COMP conclusion:

Based on the totality of European epidemiologic data for Rett Syndrome, as presented by the sponsor, the COMP considered that a population prevalence of approximately 0.5 in 10,000 people should be maintained. The RTT prevalence based on **literature ranged from 0.0030-0.60** in 10,000 people, while the one based on **European registries ranged from 0.026-0.32** in 10,000 people. Therefore, the value of approximately 0.5 per 10,000 people is considered sufficiently conservative, even when taking into account possible underdiagnosis due to variable diagnostic access and genetic confirmation across countries and/or in adults diagnosed before widespread MECP2 testing and/or incomplete registry coverage.

The accepted population prevalence of approximately 0.5 in 10,000 people is lower than previously accepted values for the condition by COMP during more recent initial orphan designation procedures (i.e. 1 in 10,000 persons EU/3/25/3081 or EU/3/25/3144). The COMP noted that these recently

accepted higher values were based on an exceptionally high value from **Norway** reported in the literature in 2012 (i.e. 1.92 per 10,000 females reported by Isaksen et al., **2012**). Therefore, the COMP considered that a value of 0.5 in 10,000 people is sufficiently conservative and likely more reflective of the actual prevalence of Rett Syndrome in the EU.

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

There are no approved therapies for the treatment of RTT in Europe.

The Consensus guidelines on managing Rett syndrome across the lifespan recommend a multidisciplinary, symptom-focused approach due to the absence of curative therapies (Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatrics Open 2020;4:e000717. doi:10.1136/ bmjpo-2020-000717, e000717.full.pdf). Management requires coordination between primary care providers and multiple specialists to address the disorder's multisystem symptom spectrum.

Key treatment domains include neurological care, particularly management of seizures, which are common and require individualized antiepileptic strategies. Respiratory and cardiac monitoring is essential due to autonomic dysfunction, including breathing irregularities and risk of cardiac abnormalities. Gastrointestinal issues, such as feeding difficulties and reflux, are managed through nutritional support and specialist input. Orthopaedic surveillance, especially for scoliosis, is also recommended.

In addition, the guidelines emphasize rehabilitative therapies, including physiotherapy, occupational therapy, and communication support, to maximize function and quality of life. Continuous, lifelong monitoring and caregiver support are critical, reflecting the chronic and complex course of RTT.

Significant benefit

Not applicable.

4. COMP position adopted on 26 June 2026

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 Rett syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to severe behavioural disturbances, locomotor disability, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased life-expectancy;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

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 Daybu, glycyl-L-2-methylprolyl-L-glutamic acid, trofinetide for treatment of Rett syndrome (EU/3/15/1534) is not removed from the Community Register of Orphan Medicinal Products.