European Union (EU) Risk Management Plan (RMP) for Daybu (trofinetide)

RMP version to be assessed as part of this application:

RMP version number:	1.0
Data lock point for this RMP:	15 November 2024
Date of final sign off:	See appended electronic signature page. Date of final sign-off for this RMP is the date for the last electronic signature.

Rationale for submitting an updated RMP:

Final RMP Version 1.0

Summary of significant changes in this RMP:

RMP Version 0.4 has been finalized and updated to RMP Version 1.0 as agreed with the PRAC Rapporteur.

Other RMP versions under evaluation:

RMP version number:	0.4
Submitted on:	24 June 2026
Procedure number:	EMEA/H/C/006482/0000

Details of the currently approved RMP:

RMP version number:	Not applicable.
Approved within procedure:	Not applicable.
Date of approval (opinion date):	Not applicable.

QPPV name: Zuzana Chomátová

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. See appended electronic signature page.

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List of Abbreviations

ALLDB	All subjects in double-blind oral treatment studies
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body Mass Index
B.V.	Besloten vennootschap
Cm	centimetre
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FXS	Fragile X syndrome
GCS	Glasgow Coma Scale
G-tube	Gastrostomy tube
GPE	Glycine-proline-glutamate
IBD	International Birth Date
IGF-1	Insulin-like Growth Factor 1
INN	International Non-proprietary Name
IV	Intravenous
Kg	kilogram
MAA	Marketing Authorization Applicant
MeCP2	methyl-CpG-binding protein 2 (in humans)
MECP2	methyl-CpG-binding protein 2 gene (in humans)
Mecp2	methyl-CpG-binding protein 2 gene (in animals)
Mecp2	methyl-CpG-binding protein 2 (in animals)
max	maximum
Mg	milligram
min	minimum
mL	millilitre
NOAEL	No Observed Adverse Effect Level
N	number
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RTT	Rett syndrome
RTTDB	Subjects with Rett syndrome in double-blind oral-treatment studies

RTTLT	Trofinetide-treated subjects with Rett syndrome in Phase 3 double-blind and open-label long-term extension studies
RTTOL	Trofinetide-treated subjects with Rett syndrome in open-label long-term extension studies
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
TBI	Traumatic brain injury
US	United States

PART I: Product(s) Overview

<table>
<tr><td>Active Substance(s)
(INN or Common Name)</td><td>Trofinetide</td></tr>
<tr><td>Pharmacotherapeutic Group(s)
(ATC Code)</td><td>N07XX24</td></tr>
<tr><td>Marketing Authorisation Applicant</td><td>Acadia Pharmaceuticals (Netherlands) B.V.</td></tr>
<tr><td>Medicinal Product(s) to Which This RMP Refers</td><td>1</td></tr>
<tr><td>Invented Name(s) in the European Economic Area (EEA)</td><td>Daybu</td></tr>
<tr><td>Marketing Authorisation Procedure</td><td>Centralised</td></tr>
<tr><td rowspan="3">Brief Description of the Product</td><td>Chemical Class
A synthetic analogue of the N-terminal tripeptide of insulin-like growth factor 1.</td></tr>
<tr><td>Summary of Mode of Action
Trofinetide is a synthetic analogue of the N-terminal tripeptide of insulin-like growth factor 1. The precise molecular mechanism of trofinetide activity in the treatment of neurobehavioural symptoms of Rett syndrome is not known.</td></tr>
<tr><td>Important Information about its Composition
<u>Excipient(s) with known effect</u>
Each mL of oral solution contains 30 mg maltitol, 1.12 mg sodium methyl parahydroxybenzoate, 0.25 mg sodium propyl parahydroxybenzoate, 4.9 mg propylene glycol, and 0.02 mg Allura Red AC.</td></tr>
<tr><td>Hyperlink to the Product Information</td><td>eCTD Module 1.3.1</td></tr>
<tr><td>Indication(s) in the EEA</td><td>Current:
Not applicable

<u>Proposed:</u>
Daybu is indicated for the treatment of neurobehavioural symptoms of Rett syndrome in adults and paediatric patients aged 5 years and older.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
Not applicable

<u>Proposed:</u>
Trofinetide should be taken twice daily, morning and evening, according to patient weight as shown in Table 1.

Table 1: Recommended dosage of trofinetide in patients 5 years of age and older
<table>
<tr><th>Patient Weight</th><th>Trofinetide dosage</th><th>Trofinetide volume</th></tr>
<tr><td>9 kg to less than 12 kg</td><td>5 g twice daily</td><td>25 mL twice daily</td></tr>
<tr><td>12 kg to less than 20 kg</td><td>6 g twice daily</td><td>30 mL twice daily</td></tr>
<tr><td>20 kg to less than 35 kg</td><td>8 g twice daily</td><td>40 mL twice daily</td></tr>
<tr><td>35 kg to less than 50 kg</td><td>10 g twice daily</td><td>50 mL twice daily</td></tr>
<tr><td>50 kg or more</td><td>12 g twice daily</td><td>60 mL twice daily</td></tr>
</table></td></tr>
</table>

	Continued benefit of treatment should be regularly re-assessed.
Pharmaceutical Form(s) and Strength(s)	**Proposed:** Oral solution. Each mL of oral solution contains 200 mg of trofinetide. **Current:** Not applicable
Is/Will the Product be Subject to Additional Monitoring in the EU?	Yes

PART II: Safety Specification

PART II: Module SI - Epidemiology of Indication(s) and Target Population(s)

Rett syndrome

Incidence:

Rett syndrome (RTT) is a seriously debilitating neurodevelopmental disorder with the incidence reported as approximately 1 in 10,000 female live births worldwide (Sampieri et al. 2007, Orphanet 2021, Petriti et al. 2023).

Prevalence:

While the prevalence of RTT in Europe is unknown, it is estimated that approximately 6,000 to 9,000 patients in the United States (US) are living with RTT (data on file).

Demographics of the Population in the Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

While the great majority of patients with RTT are females, males who meet the criteria for RTT have also been identified (Neul et al. 2019).

Risk Factors: Since RTT is a genetic disease, no typical risk factors are identified.

Main Treatment Options:

There are no approved pharmacological treatments for RTT in Europe. Treatment focuses on the management of each patient's individual symptoms and even in that regard it is often unsatisfactory and has only a limited effect on functional improvement. Accordingly, the burden on families and other caregivers is substantial (Palacios-Ceña et al. 2019).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

In approximately 96% to 98% of patients diagnosed with classic RTT, the disease is caused by mutations in the X-linked methyl-CpG-binding protein 2 gene (*MECP2*) (Percy et al. 2018). *MECP2* encodes human methyl-CpG-binding protein 2 (MeCP2), which modulates gene expression by binding to methylated CpG dinucleotides, primarily by activating but also by repressing transcription (Kriaucionis and Bird 2003, Neul et al. 2008, Hite et al. 2009, Ip et al. 2018). The activity of the MeCP2 protein is diminished in RTT in both neurons and astrocytes (Yasui et al. 2013).

Characteristic clinical features of patients with RTT include motor disability leading to limited communication, loss of hand skills, and frequent gastrointestinal symptoms, including chewing and swallowing difficulties and constipation in many patients. As such, oral administration of food and medications can be challenging. A liquid dosage form allows for weight-based dosing, as is proposed for trofinetide, and offers flexibility to dose orally in paediatric and adult patients for whom it is feasible or via G-tube, which is a common route of food and drug administration in these patients. A ready-to-use solution is preferred as it

provides convenience for caregivers and reduces complexity in usage and potential for medication errors by elimination of any additional preparation steps.

In patients with typical RTT, there is seemingly normal psychomotor development for the first 6 months of life, however; soon thereafter, the failure to reach normal developmental milestones is observed, followed by a period of developmental regression in which there is a loss of normal use of the hands and of spoken language (Samaco and Neul 2011, Neul et al. 2014). RTT is defined by characteristic clinical features, which typically include loss of verbal and nonverbal communication and voluntary motor function, characteristic repetitive hand stereotypies, and gait problems. Loss of purposeful hand use is a defining aspect of RTT during the onset of regression, and at least 30% of individuals remain without any type of purposeful hand use (Downs et al. 2010).

Other commonly observed manifestations include seizures, awake breathing disruptions, scoliosis, and intense eye communication (Neul et al. 2010). Seizures have a lifetime prevalence in RTT of around 90%. The course of seizure occurrence and remission is highly variable, with the most common pattern being waxing and waning over the lifespan. The age of first seizure onset in classic RTT ranged from immediately after birth to middle age (Tarquinio et al. 2017). Gastrointestinal dysfunction, including constipation, gastroesophageal reflux disease, and chewing and swallowing difficulties, is observed in most patients with RTT (Motil et al. 2012, Baikie et al. 2014). Autonomic manifestations, which include abnormalities in cardiac and respiratory function, as well as in peripheral circulation, are considered to be predominantly of central nervous system origin. RTT is also characterised by impaired growth affecting the brain and other organ systems.

Survival to the fifth decade is typical in RTT, and death due to extreme frailty has become rare. Lower respiratory tract infection (36.8%) was the most common cause of death, followed by aspiration/asphyxiation (31.6%), respiratory failure (14.0%), and seizure-related illness (5.3%) (Anderson et al. 2014).

While the leading cause of death remains cardiorespiratory compromise, respiratory compromise secondary to aspiration or pneumonia was also reported, and a few reports were reported at night and were unwitnessed (Tarquinio et al. 2015).

Important Co-Morbidities:

The following important co-morbidities, which also represent manifestations of the disease itself, are observed in patients with RTT (Fu et al. 2020):

- Neurological: irregular breathing patterns, epilepsy, dysphagia, sleep dysfunction, movement disorders, and behavioural disturbances
- Gastrointestinal/nutritional: constipation, gastro-oesophageal reflux, growth abnormalities, and gallbladder dysfunction
- Cardiac: prolonged QT interval
- Endocrine: low bone mineral mass, premature adrenarche or thelarche, delayed menarche, and thyroid dysfunction
- Orthopaedic: scoliosis, hip displacement, and fractures.

PART II: Module SII - Nonclinical Part of the Safety Specification

Trofinetide was evaluated in a comprehensive nonclinical safety programme that included single and repeat-dose oral and/or intravenous (IV) studies up to 4 weeks' duration and chronic oral toxicity studies up to 6 months' duration in rats and up to 9 months' duration in dogs to support oral administration to humans. Standard rodent (rat) and non-rodent (dog) species were used for toxicity and safety studies, whereas juvenile-aged and/or adult-aged animals (rats, dogs, rabbits) were used for single dose, repeat dose, and reproductive and developmental studies.

A detailed description of the non-clinical development programme for trofinetide is provided in the eCTD Module 2.4 (Nonclinical Overview).

The key safety findings from the nonclinical development programme for trofinetide are presented in Table 1.

Table 1: Key Safety Findings from the Nonclinical Development Programme for Trofinetide

Study Type	Finding	Relevance to Human Usage
Reproductive and developmental toxicity	Developmental and reproductive toxicity studies conducted with oral trofinetide included male and female rat fertility and early embryonic development studies (conducted in juvenile- and adult-aged rats), embryofoetal developmental toxicity studies in rat and rabbit, and a pre- and postnatal development toxicity study in rat. There were no adverse developmental findings noted in reproductive and developmental studies in rats or rabbits. In rats, there were no trofinetide-related effects at oral doses up to 2,000 mg/kg/day (highest dose tested) on oestrous cycling, mating, fertility, or embryonic survival in fertility and early embryonic development studies, and no maternal or developmental toxicity in embryofoetal development studies. Similarly, no developmental toxicity was noted in a rabbit embryofoetal development study at maternally tolerated doses up to 600 mg/kg/day. Oral doses of trofinetide up to 2,000 mg/kg/day in rats had no effect on viability, growth, or reproductive capacity in a peri- and postnatal development study. In the 26-week oral toxicity study conducted in juvenile-aged rats, there were no trofinetide-related adverse effects.	These studies do not raise concerns in relation to reproductive or developmental toxicity in humans.
Genotoxicity	Trofinetide was negative in in-vitro (bacterial reverse mutation, chromosomal aberration in Chinese hamster ovary cells) and in-vivo (mouse micronucleus) assays.	These studies do not raise concerns in relation to genotoxicity in humans.

Study Type	Finding	Relevance to Human Usage
Carcinogenicity	A 26-week carcinogenicity study of trofinetide in CByB6F1/TgrasH2 hemizygous transgenic mice has completed. Administration of trofinetide by twice daily oral gavage at dose levels of 300 (150 mg/kg/dose), 800 (400 mg/kg/dose), and 2000 (1000 mg/kg dose) mg/kg/day to males and 300 (150 mg/kg/dose), 600 (300 mg/kg/dose), and 200 (1000 mg/kg/dose) mg/kg/day to females for up to 26 weeks resulted in no carcinogenic effect (based on absence of any test article-related neoplastic findings), with no effects on mortality, no non-neoplastic pathology or any adverse findings related to the test article. Based on these results, the NOAEL was considered to be 2000 mg/kg/day (1000 mg/kg/dose) for both carcinogenicity and toxicity. The 24-month rat study is currently ongoing with the final report expected by July 2026.	Pharmacology and toxicology results to date with trofinetide suggest a low risk of carcinogenicity in humans.

PART II: Module SIII - Clinical Trial Exposure

The clinical development programme supporting the safety of trofinetide in RTT comprises 19 interventional clinical trials, including clinical trials in subjects with RTT, other study populations comprising subjects with neurological disorders (fragile X syndrome [FXS]) or insult (traumatic brain injury [TBI]), and healthy subjects.

The clinical safety of trofinetide in subjects with RTT include data collected in 3 double-blind, placebo-controlled studies (the pivotal Study ACP-2566-003; Study Neu-2566-RETT-002; and Study Neu-2566-RETT-001) and 3 open-label studies (Studies ACP-2566-004, ACP-2566-005, and ACP-2566-009).

Additional safety data originated from 2 double-blind, placebo-controlled studies in patients with TBI (Studies Neu-2566-TBI-001/002 and Neu-2566-TBI-003), 1 double-blind, placebo-controlled study in patients with FXS (Study Neu-2566-FXS-001), and 10 Phase 1 clinical trials in healthy or renally impaired subjects.

Detailed description of the clinical development programme for trofinetide is provided in eCTD Module 2.7.4 (Summary of Clinical Safety).

The overall safety population includes 688 subjects exposed to at least one dose of trofinetide in the above-mentioned clinical trials, including 260 subjects with RTT, 45 subjects with FXS, 186 subjects with TBI, 187 healthy volunteers, and 10 subjects with moderate renal impairment.

A summary of exposure from all clinical trials is provided by population, clinical trial, route of administration, and sex in Table 2, and by age range in Table 3.

Table 2: Cumulative Subject Exposure to Trofinetide by Population, Clinical Trial, Route of Administration, and Sex: All Interventional Clinical Trials

Population	Study Number	Number of Subjects Exposed to Trofinetide								
		IV Dosing			Oral Dosing			Overall Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total
Healthy Adult Subjects (aged 18-73)										
Healthy male subjects	Neu-2566-HV-001	20	-	20	-	-	-	20	-	20
Healthy male subjects	Neu-2566-HV-002	5	-	5	-	-	-	5	-	5
Healthy male subjects	Neu-2566-HV-003	21	-	21	-	-	-	21	-	21
Healthy female subjects	Neu-2566-HV-004	-	31	31	-	-	-	-	31	31
Healthy male and female subjects	Neu-2566-HV-005	-	-	-	9	9	18	9	9	18
Healthy male and female subjects	ACP-2566-006	-	-	-	28	13	41	28	13	41
Healthy male subjects	ACP-2566-007	-	-	-	8	-	8	8	-	8
Healthy male and female subjects	ACP-2566-008	-	-	-	12	8	20	12	8	20
Healthy male and female subjects	ACP-2566-010	-	-	-	3	7	10	3	7	10
Healthy male and female subjects	ACP-2566-012	-	-	-	13	-	13	13	-	13
Subtotal, healthy adult subjects		*46*	*31*	*77*	*73*	*37*	*110*	*119*	*68*	*187*
Moderate Renal Impairment										
Subjects with moderate renal impairment	ACP-2566-010	-	-	-	3	7	10	3	7	10
Subtotal, adult subjects with moderate renal impairment		-	-	-	3	7	10	3	7	10
Rett Syndrome (aged 2-40)										
Adolescent and adult female RTT patients (aged 15-40)	Neu-2566-RETT-001	-	-	-	-	35	35	-	35	35
Child and adolescent female RTT patients (aged 5-15)	Neu-2566-RETT-002	-	-	-	-	58	58	-	58	58
Child, adolescent, and adult female RTT patients (aged 5-20)	ACP-2566-003	-	-	-	-	93[a]	93[a]	-	93[a]	93[a]
Subtotal, subjects with RTT (double-blind studies, unique subjects)		-	-	-	-	*176[a]*	*176[a]*	-	*176[a]*	*176[a]*
Child, adolescent, and adult female RTT patients (aged 5-21)	ACP-2566-004	-	-	-	-	154[b]	154[b]	-	154[b]	154[b]
Child, adolescent, and adult female RTT patients (aged 6-20)	ACP-2566-005	-	-	-	-	*77[c]*	*77[c]*	-	*77[c]*	*77[c]*
Female RTT patients (aged 2-4)	ACP-2566-009	-	-	-	-	15	15	-	15	15
Subtotal, subjects with RTT (double-blind and open-label studies, unique subjects)		-	-	-	-	*260[c]*	*260[c]*	-	*260[b, c]*	*260[c]*
Fragile X Syndrome										
Adolescent and adult male FXS patients (aged 13-41)	Neu-2566-FXS-001	-	-	-	45	-	45	45	-	45

Population	Study Number	Number of Subjects Exposed to Trofinetide								
		IV Dosing			Oral Dosing			Overall Total		
		Male	Female	Total	Male	Female	Total	Male	Female	Total
Subtotal, subjects with FXS		-	-	-	*45*	-	*45*	*45*	-	*45*
Traumatic Brain Injury										
Patients with moderate to severe TBI (GCS 4-12) (aged 16-68)	Neu-2566-TBI-001/002	143	24	167	-	-	-	143	24	167
Patients with mild TBI (GCS 13-15) (aged 19-40)	Neu-2566-TBI-003	-	-	-	15	4	19	15	4	19
Subtotal, subjects with TBI		*143*	*24*	*167*	*15*	*4*	*19*	*158*	*28*	*186*
Total number of unique subjects, all studies		**189**	**55**	**244**	**136**	**308**	**444**	**325**	**363**	**688**

Source: Module 2.7.4, Table 2.7.4-5

[a] The 93 subjects who received trofinetide in Study ACP-2566-003 includes 10 subjects who were also exposed to trofinetide in Study Neu-2566-RETT-002.

[b] The 154 subjects who received trofinetide in Study ACP-2566-004 includes 69 subjects who were also exposed to trofinetide in Study ACP-2566-003, and 16 subjects who were also exposed to trofinetide in Study Neu-2566-RETT-002.

[c] The 77 subjects who received trofinetide in Study ACP-2566-005 were all exposed to trofinetide in Study ACP-2566-004.

Abbreviations: FXS, fragile X syndrome; GCS, Glasgow Coma Scale; IV, intravenous; RTT, Rett syndrome; TBI, traumatic brain injury.

Table 3: Cumulative Subject Exposure to Trofinetide by Population, Route of Administration, and Age Group: All Interventional Clinical Trials

Population	Number of Subjects Exposed to Trofinetide																		
	Intravenous Dosing						Oral Dosing						Overall Total						
	Age 2-4	Age 5-11	Age 12-17	Age 18-45	Age 46-64	Age ≥65	Age 2-4	Age 5-11	Age 12-17	Age 18-45	Age 46-64	Age ≥65	Age 2-4	Age 5-11	Age 12-17	Age 18-45	Age 46-64	Age ≥65	Total
Healthy adult subjects (male and female, ages 18-73)	-	-	-	77	-	-	-	-	-	101	5	4	-	-	-	178	5	4	187
Moderate renal impairment (ages 46-74)	-	-	-	-	-	-	-	-	-	-	5	5	-	-	-	-	5	5	10
Rett syndrome[a] (female, ages 2-40)	-	-	-	-	-	-	15	134	65	46	-	-	15	134	65	46	-	-	260
Fragile X syndrome (male, ages 12-41)	-	-	-	-	-	-	-	-	15	30	-	-	-	-	15	30	-	-	45
Traumatic brain injury (male and female, ages 16-68)	-	-	6	118	40	3	-	-	-	19	-	-	-	-	6	137	40	3	186
Total number of subjects, all studies	**-**	**-**	**6**	**195**	**40**	**3**	**15**	**134**	**80**	**196**	**10**	**9**	**15**	**134**	**86**	**391**	**50**	**12**	**688**

Source: Module 2.7.4, Table 2.7.4-6

[a] Unique subjects; for subjects participating in more than one of the Studies ACP-2566-002, -003, -004 or -005, ages are at Screening (Baseline for ACP-2566-004) of the earliest study where the subject received trofinetide.

The clinical safety data from the clinical development programme for trofinetide was integrated and analysed across 4 pools, representing both randomised double-blind studies in RTT, FXS, and TBI, and open-label long-term studies in RTT (Table 4). Of these, the subjects with RTT in double-blind oral-treatment studies (RTTDB) Pool and the trofinetide-treated subjects with RTT in Phase 3 double-blind and open-label long-term extension studies (RTTLT) Pool represent the populations of primary interest in subjects with RTT.

Table 4: Safety Data Pooling Strategy

Pooled Population	**Description** **Study Numbers**
RTTDB	Placebo-controlled, double-blind data in RTT – ACP-2566-003 – Neu-2566-RETT-001 – Neu-2566-RETT-002
ALLDB	Placebo-controlled, double-blind data in all indications – ACP-2566-003 – Neu-2566-RETT-001 – Neu-2566-RETT-002 – Neu-2566-TBI-003 – Neu-2566-FXS-001
RTTLT	RTT Phase 3, long-term data – ACP-2566-003 – ACP-2566-004 – ACP-2566-005
RTTOL	RTT Phase 3, long-term, open-label data – ACP-2566-004 – ACP-2566-005

Source: Module 2.7.4, Tables 2.7.4-2, 2.7.4-7, 2.7.4-8, 2.7.4-9, and 2.7.4-10.
Abbreviations: ALLDB, all subjects in double-blind oral-treatment studies; BID, twice daily; RTT, Rett syndrome; RTTDB, subjects with Rett syndrome in double-blind oral-treatment studies; RTTLT, trofinetide-treated subjects with Rett syndrome in Phase 3 double-blind and open-label long-term extension studies; RTTOL, trofinetide-treated subjects with Rett syndrome in open-label long-term extension studies.

An overview of the duration of exposure to trofinetide from the clinical development programme is provided for the RTTDB Pool in Table 5, all subjects in double-blind oral-treatment studies (ALLDB) Pool in Table 6, RTTLT Pool in Table 7, and trofinetide-treated subjects with RTT in open-label long-term extension studies (RTTOL) Pool in Table 8.

The demographic and baseline characteristics of subjects in the clinical development programme are provided for the RTTDB Pool in Table 9, ALLDB Pool in Table 10, RTTLT Pool in Table 11, and the RTTOL Pool in Table 12.

Table 5: Study Drug Exposure – RTTDB Pool

	Placebo (N = 133)	Trofinetide			Study ACP-2566-003[a]	
		<200 mg/kg BID (N = 67)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 176)	Placebo (N = 94)	Trofinetide (N = 93)
Duration of Double-Blind Exposure (Days)[b]						
n	133	67	115	176	94	93
Mean (SE)	69.0 (2.47)	33.0 (1.19)	68.8 (2.39)	57.5 (2.21)	81.5 (1.66)	73.5 (2.50)
SD	28.46	9.72	25.67	29.27	16.07	24.14
Median	85.0	28.0	84.0	42.0	85.0	85.0
Minimum, maximum	10, 128	1, 43	8, 124	1, 130	10, 100	8, 93
Duration of Double-Blind Exposure - Categorical, n (%)						
<1 week	-	1 (1.5)	-	1 (0.6)	-	-
≥1 week to <2 weeks	1 (0.8)	-	6 (5.2)	5 (2.8)	1 (1.1)	6 (6.5)
≥2 weeks to <6 weeks	23 (17.3)	36 (53.7)	7 (6.1)	43 (24.4)	3 (3.2)	8 (8.6)
≥6 weeks to <12 weeks	28 (21.1)	30 (44.8)	33 (28.7)	57 (32.4)	9 (9.5)	12 (12.9)
≥12 weeks	81 (60.9)	-	69 (60.0)	70 (39.8)	81 (86.2)	67 (72.0)

Source: Module 2.7.4, Table 2.7.4-7

Notes: The RTTDB Pool includes Studies ACP-2566-003, Neu-2566-RETT-002, and Neu-2566-RETT-001.
A total of 39 subjects were enrolled in both Study Neu-2566-RETT-002 and the pivotal Study ACP-2566-003.
Subjects can be counted in multiple dose/drug columns if a different dose/drug was administered in these studies. However, these subjects are only counted once in the placebo or all trofinetide column.
N is used as the denominator for calculating percentages within each column.

[a] Subjects who received trofinetide in Study ACP-2566-003 are also included in the ≥200 to 500 mg/kg BID and the All Trofinetide columns. Subjects who received placebo in Study ACP-2566-003 are also included in the All Placebo group.

[b] Duration of exposure to double-blind study drug within each study is calculated as last double-blind study dose date - first double-blind study dose date +1.

Abbreviations: BID, twice daily; RTTDB, Rett syndrome in double-blind oral-treatment studies; SD, standard deviation; SE, standard error of the mean.

Table 6: Study Drug Exposure – ALLDB Pool

	Trofinetide				Study ACP-2566-003[a]	
	Placebo (N = 168)	<200 mg/kg BID (N = 131)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 240)	Placebo (N = 94)	Trofinetide (N = 93)
Duration of Double-Blind Exposure (Days)[b]						
N	168	131	115	240	94	93
Mean (SE)	58.9 (2.50)	27.4 (0.98)	68.8 (2.39)	47.9 (1.94)	81.5 (1.66)	73.5 (2.50)
SD	32.35	11.17	25.67	30.10	16.07	24.14
Median	83.0	28.0	84.0	42.0	85.0	85.0
Minimum, maximum	2, 128	1, 43	8, 124	1, 130	10, 100	8, 93
Duration of Double-Blind Exposure - Categorical, n (%)						
<1 week	2 (1.2)	2 (1.5)	-	2 (0.8)	-	-
≥1 week to <2 weeks	10 (6.0)	18 (13.7)	6 (5.2)	23 (9.6)	1 (1.1)	6 (6.5)
≥2 weeks to <6 weeks	47 (28.0)	81 (61.8)	7 (6.1)	88 (36.7)	3 (3.2)	8 (8.6)
≥6 weeks to <12 weeks	28 (16.7)	30 (22.9)	33 (28.7)	57 (23.8)	9 (9.5)	12 (12.9)
≥12 weeks	81 (48.2)	-	69 (60.0)	70 (29.2)	81 (86.2)	67 (72.0)

Source: Module 2.7.4, Table 2.7.4-8

Notes: The ALLDB Pool includes Studies ACP-2566-003, Neu-2566-RETT-002, Neu-2566-RETT-001, Neu-2566-TBI-003, and Neu-2566-FXS-001. A total of 39 subjects were enrolled in both Study RETT-002 and the pivotal Study ACP-2566-003. Subjects can be counted in multiple trofinetide dose columns if a different dose was administered in these studies. These subjects are only counted once in the All Trofinetide column. N is used as the denominator for calculating percentages within each column.

[a] Subjects who received trofinetide in Study ACP-2566-003 are also included in the ≥200 to 500 mg/kg BID and the All Trofinetide columns. Subjects who received placebo in Study ACP-2566-003 are also included in the All Placebo group.

[b] Duration of exposure to double-blind study drug within each study is calculated as last double-blind study dose date - first double-blind study dose date +1.

Abbreviations: ALLDB, all subjects in double-blind oral-treatment studies; BID, twice daily; FXS, fragile X syndrome; SD, standard deviation; SE, standard error of the mean; TBI, traumatic brain injury.

Table 7: Study Drug Exposure – RTTLT Pool

	All Trofinetide (N = 178)
Duration of Open-label Exposure (Days)[a]	
n	178
Mean (SE)	396.6 (25.83)
SD	344.60
Median	260.0
Minimum, maximum	8, 1190
Duration of Open-label Exposure – Categorical, n (%)	
<6 weeks	23 (12.9)
≥6 weeks to <12 weeks	21 (11.8)
≥12 weeks to <6 months	34 (19.1)
≥6 months to <9 months	13 (7.3)
≥9 months to <12 months	7 (3.9)
≥12 months to <18 months	12 (6.7)
≥18 months to <24 months	24 (13.5)
≥24 months	44 (24.7)

Source: Module 2.7.4, Table 2.7.4-9

Note: N is used as the denominator for calculating percentages within each column.

[a] Duration of exposure to trofinetide within each study is calculated as last trofinetide dose date – first trofinetide dose date +1. For a given subject, the total duration of trofinetide exposure is calculated as the sum of trofinetide exposure durations from all studies in which the subject received trofinetide. For Studies ACP-2566-004 or ACP-2566-005, if a subject was still alive and ongoing at the time of data cut, the last dose date was imputed as the data cut date.

Abbreviations: RTTLT, trofinetide-treated subjects with Rett syndrome in Phase 3 double-blind and open-label long-term extension studies; SD, standard deviation; SE, standard error of the mean.

Table 8: Study Drug Exposure – RTTOL Pool

	All Trofinetide (N = 154)
Total duration of exposure (days)[a]	
n	154
Mean (SE)	414.3 (26.44)
SD	328.14
Median	303.5
Minimum, maximum	8, 1106
Total duration of exposure - categorical, n (%)	
<6 weeks	17 (11.0)
≥6 weeks to <12 weeks	22 (14.3)
≥12 weeks to <6 months	18 (11.7)
≥6 months to <9 months	12 (7.8)
≥9 months to <12 months	10 (6.5)
≥12 months to <18 months	7 (4.5)
≥18 months to <24 months	33 (21.4)
≥24 months	35 (22.7)

Source: Table RTTOL.MAA.4

Note: N is used as the denominator for calculating percentages within each column.

[a] Duration of exposure to trofinetide within each study is calculated as last trofinetide dose date - first trofinetide dose date +1. If a subject experienced continuous study drug interruption for more than 30 days, the duration of exposure was calculated as last trofinetide dose date – first trofinetide dose date + 1 – duration of interruption. For a given subject, the total duration of trofinetide exposure is calculated as the sum of trofinetide exposure durations from all open-label extension studies in which the subject received trofinetide. For Studies ACP-2566-004 or ACP-2566-005, if a subject was still alive and ongoing at the time of data cut, the last dose date was imputed as the data cut date.

Abbreviations: RTTOL, trofinetide-treated subjects with Rett syndrome in open-label long-term extension studies; SD, standard deviation; SE, standard error of the mean.

Table 9: Demographics and Baseline Characteristics – RTTDB Pool

		Trofinetide			ACP-2566-003[a]	
	Placebo (N = 133)	<200 mg/kg BID (N = 67)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 176)	Placebo (N = 94)	Trofinetide (N = 93)
Sex, n (%)						
Female	133 (100.0)	67 (100.0)	115 (100.0)	176 (100.0)	94 (100.0)	93 (100.0)
Age (years)						
n	133	67	115	176	94	93
Mean (SE)	13.0 (0.68)	17.2 (1.03)	10.5 (0.42)	13.1 (0.54)	10.9 (0.47)	11.0 (0.49)
SD	7.82	8.40	4.53	7.10	4.57	4.69
Median	11.0	17.0	10.0	12.0	10.0	10.0
Min, Max	5, 44	5, 40	5, 20	5, 40	5, 20	5, 20
Age categories, n (%)						
5 to <12 years	69 (51.9)	20 (29.9)	69 (60.0)	85 (48.3)	55 (58.5)	53 (57.0)
12 to <17 years	30 (22.6)	13 (19.4)	30 (26.1)	41 (23.3)	24 (25.5)	23 (24.7)
≥17 years	34 (25.6)	34 (50.7)	16 (13.9)	50 (28.4)	15 (16.0)	17 (18.3)
Country, n (%)						
United States	133 (100.0)	67 (100.0)	115 (100.0)	176 (100.0)	94 (100.0)	93 (100.0)
Primary race, n (%)						
White	126 (94.7)	61 (91.0)	102 (88.7)	157 (89.2)	90 (95.7)	82 (88.2)
Black or African American	[redacted]	5 (7.5)	[redacted]	6 (3.4)	[redacted]	[redacted]
Asian	[redacted]	[redacted]	7 (6.1)	8 (4.5)	[redacted]	5 (5.4)
American Indian or Alaska Native	-	-	-	-	-	-
Native Hawaiian or other Pacific Islander	-	-	[redacted]	[redacted]	-	[redacted]
Other	3 (2.3)	-	4 (3.5)	4 (2.3)	[redacted]	4 (4.3)
White	126 (94.7)	61 (91.0)	102 (88.7)	157 (89.2)	90 (95.7)	82 (88.2)
Non-white	7 (5.3)	6 (9.0)	13 (11.3)	19 (10.8)	4 (4.3)	11 (11.8)
Ethnicity, n (%)						
Hispanic or Latino	13 (9.8)	4 (6.0)	12 (10.4)	15 (8.5)	10 (10.6)	7 (7.5)
Not Hispanic or Latino	120 (90.2)	62 (92.5)	103 (89.6)	160 (90.9)	84 (89.4)	86 (92.5)
Not Reported	-	[redacted]	-	[redacted]	-	-
Height (cm)						
n	130	66	114	174	92	92
Mean (SE)	129.2 (1.37)	132.7 (1.60)	127.0 (1.51)	129.1 (1.17)	127.6 (1.67)	128.4 (1.70)
SD	15.60	13.04	16.14	15.47	15.97	16.28
Median	129.1	137.2	127.1	129.6	127.6	128.1
Min, Max	92, 171	104, 162	94, 170	94, 170	92, 171	94, 170
Weight (kg)						
n	133	67	115	176	94	93
Mean (SE)	30.6 (1.00)	35.8 (1.73)	29.3 (1.10)	31.8 (0.99)	29.2 (1.07)	30.5 (1.31)
SD	11.48	14.12	11.79	13.17	10.37	12.61
Median	28.8	34.0	26.0	30.7	27.3	29.6
Min, Max	13, 76	17, 79	13, 61	13, 79	13, 57	13, 78
BMI (kg/m²)						
n	130	66	114	174	91	92
Mean (SE)	17.711 (0.3505)	20.027 (0.8156)	17.424 (0.3723)	18.483 (0.4000)	17.2 (0.36)	17.820 (0.46)

		Trofinetide			ACP-2566-003[a]	
	Placebo (N = 133)	<200 mg/kg BID (N = 67)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 176)	Placebo (N = 94)	Trofinetide (N = 93)
SD	3.9968	6.6261	3.9747	5.2764	3.46	4.43
Median	16.876	18.011	16.905	17.261	16.6	16.8
Min, Max	11.60, 34.10	10.90, 46.14	10.64, 31.18	10.64, 46.14	12, 28	10, 34

Source: Module 2.7.4, Table 2.7.4-15

Notes: The RTTDB Pool includes Studies ACP-2566-003, Neu-2566-RETT-002, and Neu-2566-RETT-001. Subjects can be counted in multiple dose/drug columns if a different dose/drug was administered in these studies. However, these subjects are only counted once in the placebo or all trofinetide column.

N is used as the denominator for calculating percentages within each column.

[a] Subjects who received trofinetide in Study ACP-2566-003 are also included in the ≥200 to 500 mg/kg BID and the All Trofinetide columns. Subjects who received placebo in Study ACP-2566-003 are also included in the All Placebo group.

Abbreviations: BID, twice daily; BMI, body mass index; Max, maximum; Min, minimum; RTTDB, Rett syndrome in double-blind oral-treatment studies; SD, standard deviation; SE, standard error of the mean.

Table 10: Demographics and Baseline Characteristics – ALLDB Pool

		Trofinetide			ACP-2566-003[a]	
	Placebo (N = 168)	<200 mg/kg BID (N = 131)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 240)	Placebo (N = 94)	Trofinetide (N = 93)
Sex, n (%)						
Female	133 (79.2)	71 (54.2)	115 (100.0)	180 (75.0)	94 (100.0)	93 (100.0)
Male	35 (20.8)	60 (45.8)	-	60 (25.0)	-	-
Age (years)						
n	168	131	115	240	94	93
Mean (SE)	14.8 (0.65)	21.0 (0.78)	10.5 (0.42)	16.2 (0.58)	10.9 (0.47)	11.0 (0.49)
SD	8.41	8.96	4.53	8.97	4.57	4.69
Median	13.0	20.0	10.0	14.0	10.0	10.0
Min, Max	5, 44	5, 40	5, 20	5, 40	5, 20	5, 20
Age categories, n (%)						
5 to <12 years	69 (41.1)	20 (15.3)	69 (60.0)	85 (35.4)	55 (58.5)	53 (57.0)
12 to <17 years	40 (23.8)	24 (18.3)	30 (26.1)	52 (21.7)	24 (25.5)	23 (24.7)
≥17 years	59 (35.1)	87 (66.4)	16 (13.9)	103 (42.9)	15 (16.0)	17 (18.3)
Country, n (%)						
United States	168 (100.0)	131 (100.0)	115 (100.0)	240 (100.0)	94 (100.0)	93 (100.0)
Primary race, n (%)						
White	153 (91.1)	114 (87.0)	102 (88.7)	210 (87.5)	90 (95.7)	82 (88.2)
Black or African American	6 (3.6)	10 (7.6)	[redacted]	11 (4.6)	[redacted]	[redacted]
Asian	[redacted]	[redacted]	7 (6.1)	9 (3.8)	[redacted]	5 (5.4)
American Indian or Alaska Native	[redacted]	[redacted]	-	[redacted]	-	-
Native Hawaiian or other Pacific Islander	-	-	[redacted]	[redacted]	-	[redacted]
Other	5 (3.0)	4 (3.1)	4 (3.5)	8 (3.3)	[redacted]	4 (4.3)
White	153 (91.1)	114 (87.0)	102 (88.7)	210 (87.5)	90 (95.7)	82 (88.2)
Non-white	15 (8.9)	17 (13.0)	13 (11.3)	30 (12.5)	4 (4.3)	11 (11.8)
Ethnicity, n (%)						
Hispanic or Latino	17 (10.1)	9 (6.9)	12 (10.4)	20 (8.3)	10 (10.6)	7 (7.5)
Not Hispanic or Latino	151 (89.9)	120 (91.6)	103 (89.6)	218 (90.8)	84 (89.4)	86 (92.5)
Not Reported	-	[redacted]	-	[redacted]	-	-
Height (cm)						
n	165	130	114	238	92	92
Mean (SE)	137.2 (1.75)	151.9 (2.11)	127.0 (1.51)	140.5 (1.58)	127.6 (1.67)	128.4 (1.70)
SD	22.51	24.11	16.14	24.38	15.97	16.28
Median	135.0	151.7	127.1	137.2	127.6	128.1
Min, Max	68, 183	70, 191	94, 170	70, 191	92, 171	94, 170
Weight (kg)						
n	168	131	115	240	94	93
Mean (SE)	40.5 (1.79)	58.3 (2.52)	29.3 (1.10)	45.2 (1.74)	29.2 (1.07)	30.5 (1.31)
SD	23.20	28.82	11.79	26.90	10.37	12.61
Median	34.5	56.3	26.0	36.4	27.3	29.6
Min, Max	13, 106	17, 142	13, 61	13, 142	13, 57	13, 78

		Trofinetide			ACP-2566-003[a]	
	Placebo (N = 168)	<200 mg/kg BID (N = 131)	≥200 to 500 mg/kg BID (N = 115)	All Trofinetide (N = 240)	Placebo (N = 94)	Trofinetide (N = 93)
BMI (kg/m²)						
n	165	130	114	238	91	92
Mean (SE)	20.438 (0.8857)	24.684 (1.4129)	17.424 (0.3723)	21.442 (0.8229)	17.2 (0.36)	17.820 (0.46)
SD	11.3770	16.1091	3.9747	12.6950	3.46	4.43
Median	17.867	23.476	16.905	18.957	16.6	16.8
Min, Max	11.60, 146.41	10.90, 188.78	10.64, 31.18	10.64, 188.78	12, 28	10, 34

Source: Module 2.7.4, Table 2.7.4-16

Notes: The ALLDB Pool includes Studies ACP-2566-003, Neu-2566-RETT-002, Neu-2566-RETT-001, Neu2566-TBI-003, and Neu-2566-FXS-001. Subjects can be counted in multiple trofinetide dose columns if a different dose was administered in these studies. These subjects are only counted once in the All Trofinetide column.

N is used as the denominator for calculating percentages within each column.

[a] Subjects who received trofinetide in Study ACP-2566-003 are also included in the ≥200 to 500 mg/kg BID and the All Trofinetide columns. Subjects who received placebo in Study ACP-2566-003 are also included in the All Placebo group.

Abbreviations: ALLDB, all subjects in double-blind oral-treatment studies; BID, twice daily; BMI, body mass index; cm, centimetre; kg, kilogram; m, meter; Max, maximum; Min, minimum; n, number; SD, standard deviation; SE, standard error.

Table 11: Demographics and Baseline Characteristics – RTTLT Pool

	All Trofinetide (N = 178)
Sex, n (%)	
Female	178 (100.0)
Age (years)[a]	
n	178
Mean (SE)	11.0 (0.34)
SD	4.59
Median	10.0
Minimum, maximum	5, 21
Age categories, n (%)[a]	
5 to <12 years	104 (58.4)
12 to <17 years	43 (24.2)
≥17 years	31 (17.4)
Country, n (%)	
United States	178 (100.0)
Primary race, n (%)	
White	164 (92.1)
Black or African American	[redacted]
Asian	6 (3.4)
American Indian or Alaska Native	-
Native Hawaiian or other Pacific Islander	[redacted]
Other	6 (3.4)
White	164 (92.1)
Non-white	14 (7.9)
Ethnicity, n (%)	
Hispanic or Latino	16 (9.0)
Not Hispanic or Latino	162 (91.0)
Height (cm)[b]	
n	176
Mean (SE)	128.7 (1.18)
SD	15.68
Median	128.0
Minimum, maximum	94, 170
Weight (kg)[b]	
n	178
Mean (SE)	30.1 (0.88)
SD	11.69
Median	28.3
Minimum, maximum	12, 78

	All Trofinetide (N = 178)
BMI (kg/m²)[b]	
n	176
Mean (SE)	17.478 (0.2943)
SD	3.9049
Median	16.831
Minimum, maximum	10.64, 34.85

Source: Module 2.7.4, Table 2.7.4-17
Notes: The RTTLT Pool includes Studies ACP-2566-003, ACP-2566-004, and ACP-2566-005.
N is used as the denominator for calculating percentages within each column.
[a] The baseline age was based on the baseline age in Study ACP-2566-003, regardless of whether a subject received the first trofinetide dose in Study ACP-2566-003 or ACP-2566-004.
[b] Last height, weight, and BMI measured before receiving the first trofinetide dose.
Abbreviations: BMI, body mass index; RTTLT, trofinetide-treated subjects with Rett syndrome in Phase 3 double-blind and open-label long-term extension studies; SD, standard deviation; SE, standard error of the mean.

Table 12: Demographics and Baseline Characteristics – RTTOL Pool

	All Trofinetide (N = 154)
Sex, n (%)	
Female	154 (100.0)
Age (years)[a]	
n	154
Mean (SE)	11.0 (0.37)
SD	4.55
Median	10.0
Minimum, maximum	5, 21
Age categories, n (%)[a]	
5 to <12 years	92 (59.7)
12 to <17 years	37 (24.0)
≥17 years	25 (16.2)
Country, n (%)	
United States	154 (100.0)
Primary race, n (%)	
White	143 (92.9)
Black or African American	[redacted]
Asian	5 (3.2)
American Indian or Alaska Native	- -
Native Hawaiian or other Pacific Islander	[redacted]
Other	4 (2.6)
White	143 (92.9)
Non-white	11 (7.1)
Ethnicity, n (%)	
Hispanic or Latino	14 (9.1)
Not Hispanic or Latino	140 (90.9)
Height (cm)[b]	
n	152
Mean (SE)	128.6 (1.22)
SD	15.05
Median	128.1
Minimum, maximum	96, 164
Weight (kg)[b]	
n	154
Mean (SE)	29.3 (0.87)
SD	10.78
Median	27.8
Minimum, maximum	12, 60
BMI (kg/m²)[b]	
n	152
Mean (SE)	17.032 (0.2828)
SD	3.4865
Median	16.642
Minimum, maximum	10.39, 28.86

Source: Table RTTOL.MAA.2

Note: N is used as the denominator for calculating percentages within each column.

[a] The baseline age was based on the baseline age in Study ACP-2566-004.

[b] Last height, weight, and BMI measured before receiving the first trofinetide dose.

Abbreviations: BMI, body mass index; RTTOL, trofinetide-treated subjects with Rett syndrome in open-label long-term extension studies; SD, standard deviation; SE, standard error of the mean

PART II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 13: Important Exclusion Criteria from Pivotal Clinical Trials

Criteria	Reason for Exclusion	Is It Considered To Be Included As Missing Information?
Children below 9 kg	Children with RTT aged 2 years and older are generally not below 9 kg.	No **Rationale:** Not relevant for the target population
Pregnant women	Pregnant women are usually excluded from clinical studies even if there is no evidence of potential harm to foetuses. Patients with RTT very rarely if ever become pregnant.	No **Rationale:** Not relevant for the target population
Breastfeeding women	Breastfeeding women are usually excluded from clinical studies even if there is no evidence of potential harm to foetuses. Patients with RTT very rarely if ever become pregnant.	No **Rationale:** Not relevant for the target population
Elderly (65 years and older)	Trofinetide has not been studied in elderly patients, due to the low prevalence.	No **Rationale:** It is not anticipated that trofinetide will be used in this population. The safety profile of trofinetide is not expected to differ in elderly patients.
Severe renal impairment	Since the drug is eliminated mainly through the kidney, administration of trofinetide to patients with severe renal impairment is not recommended.	No **Rationale:** Not relevant for the target population
Clinically significant conditions: – Cardiovascular – Endocrine (such as hypo- or hyperthyroidism, Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus), – Hearing impairment, – Hepatic disease, – Respiratory disease, – Gastrointestinal disease (such as celiac disease or inflammatory bowel disease), – Cerebrovascular disease or brain trauma, – Malignancy.	These conditions could confound results comparing trofinetide with placebo by introducing variability.	No **Rationale:** Use in these populations is not predicted to be associated with additional risks of clinical significance.

Abbreviation: RTT, Rett syndrome

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

There were no inherent limitations introduced by the clinical study design that would prevent the collection of adverse reactions. However, due to the low number of patients with targeted rare diseases in the Daybu clinical trials, the clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 14: Exposure to Trofinetide in Special Populations Within the Target Population

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Patients with hepatic impairment	Not included in the clinical development programme. Hepatic impairment is not expected to impact the exposure of trofinetide because hepatic metabolism is not a significant route of trofinetide elimination.
• Patients with renal impairment	Ten (10) male and female otherwise healthy subjects (aged 46-74 years) with moderate renal impairment were included in the Phase 1 Study ACP-2566-010. Subjects with severe renal impairment were not included in the clinical development program.
• Patients with other clinically significant comorbidities (e.g., cardiovascular, respiratory)	Not included in the clinical development programme.
Other • Males	Not included in the RTT studies.
• Elderly (65 years and older)	Not included in the clinical development programme.
• Children below 9 kg	Not included in the clinical development programme.

Abbreviations: kg, kilogram; RTT, Rett syndrome

PART II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Trofinetide was first approved in the US under the trade name Daybue on 10 March 2023, which represents the international birth date (IBD) for trofinetide.

Trofinetide is currently approved in the US and Canada, and is actively marketed in the US. Since submission of the initial MAA, trofinetide has had limited commercial distribution in Canada and has been distributed outside North America through early access and named patient programs.

The estimated post-marketing exposure to trofinetide is therefore based on the number of bottles commercially distributed in the US and the recommended trofinetide posology from 50 mL/day to 120 mL/day.

SV.1.2 Exposure

Since the IBD until 15 November 2024, [redacted] bottles of Daybue (trofinetide) were commercially distributed in the US, representing [redacted] patient-years (at 120 mL/day) to [redacted] patient-years (at 50 mL/day) of trofinetide treatment.

Since IBD until 15 November 2024, an estimated [redacted] new patients with RTT received Daybue (trofinetide) commercially in the US.

PART II: Module SVI - Additional EU Requirements for Safety Specification

Potential for Misuse for Illegal Purposes

Considering the mechanism of action of trofinetide, the potential for misuse for illegal purposes is negligible and does not constitute a safety concern.

PART II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

- Potential Risk with Minimal Clinical Impact on Patients (in Relation to the Severity of the Indication Treated):
    - Liver function test elevations

In general, for both chemistry and haematology laboratory parameters, mean changes from baseline to overall postbaseline maximum did not appear clinically significant. The percentage of subjects with potentially clinically important chemistry or haematology values at any postbaseline visit was generally small and similar between the All Trofinetide and Placebo groups.

In the RTTDB Pool, the percentage of subjects with potentially clinically important alanine aminotransferase (ALT) values (≥3 × upper limit of normal [ULN]) were 4.0% and 2.3% in the All Trofinetide and Placebo groups, respectively.

In the RTTLT Pool, 7.1% of subjects had potentially clinically important ALT values.

No subjects in the RTTDB or RTTLT Pools had an AST and/or ALT value ≥5 × ULN or ≥10 × ULN. No subjects met Hy's law criteria for drug-induced liver injury (defined as ALT or AST ≥3× ULN, ALP <2 × ULN, and bilirubin ≥2 × ULN).

Overall, ALT and other liver function test changes were mild, transient, occurred early on after starting treatment with trofinetide, and were self-limited while still on drug. There was a single discontinuation due to elevated ALT and for that case the value (77 U/L) was neither clinically significant nor potentially clinically important.

For subjects with potentially clinically important ALT values, there were no clinical symptoms indicating liver injury (abdominal pain, jaundice). Consistent with the tendency of elevated ALT to appear early on after initial treatment with trofinetide, and to be self-limited, there were only a few post-baseline potentially clinically important liver function test values observed in Study ACP-2566-005, in which subjects had already been treated with trofinetide for at least 40 weeks.

- Adverse Reactions with Clinical Consequences, Even Serious, But Occurring with a Low Frequency and Considered to Be Acceptable in Relation to the Severity of the Targeted Indication Treated:
    - Seizure

Seizures and epilepsy are common in RTT. In a large longitudinal study of the course of epilepsy in RTT patients followed longitudinally for up to 9.0 years, the estimated cumulative lifetime prevalence of epilepsy in RTT approached 90%, with many clinical features being associated with the development of seizures. The age of first seizure onset in classic RTT ranged from immediately after birth to 46.8 years. Onset occurs in the first decade of life in most patients: 25% developed epilepsy by age 3.0 years, 50% by 5.9 years, and 75% by 13.2 years. Among RTT subjects who entered the study without a history of seizures, 32.3% experienced their first seizure during the study. In the same longitudinal study, three distinct patterns of seizure prevalence emerged in classic RTT, including those who did not have seizures throughout the study (30% of the sample), those who had frequent relapse and remission (54%), and those who had relentless seizures (16%), for most patients with RTT who develop epilepsy, the timing of seizure onset and relapse cannot be reliably anticipated(Tarquinio et al. 2017).

In the RTTDB Pool, the incidence of seizure treatment-emergent adverse events (TEAEs) was similar across groups, with 5.7% (10 of 176 subjects) in the All Trofinetide group and 6.0% (8 of 133 subjects) in the Placebo group. Seizure TEAEs considered by the Investigator to be related to study drug occurred in 2 (1.1%) subjects in the All Trofinetide group and in 1 (0.8%) subject in the Placebo group. Most events of seizure were mild or moderate in severity. One subject in the All Trofinetide group had a severe TEAE of seizure cluster and 1 subject in the Placebo group had a severe TEAE of seizure. Two subjects in the All Trofinetide group had TEAEs of seizure that led to study discontinuation. No subjects in the Placebo group discontinued due to seizures. In the All Trofinetide group, 1 subject had a serious TEAE of seizure and 1 subject had a serious TEAE of tonic convulsion. No subjects in the Placebo group experienced a serious TEAE of seizure.

In the RTTLT Pool, 28 (15.7%) subjects experienced a TEAE under the convulsions SMQ. Of these, 6 (3.4%) subjects had seizure and 1 (0.6%) subject had seizure cluster considered by the Investigator to be related to study drug. Nine (5.1%) subjects had serious seizure, 3 (1.7%) subjects had serious status epilepticus, 1 (0.6%) subject had serious generalised tonic-clonic seizure, and 1 (0.6%) subject experienced sudden unexplained death in epilepsy. Five (2.8%) subjects (2.8%) had seizure and 2 (1.1%) subjects had seizure cluster that led to study discontinuation. In addition, 1 subject (0.6%) experienced sudden unexplained death in epilepsy (mentioned above).

- Vomiting, including aspiration and aspiration pneumonia

Vomiting was the second most commonly reported TEAE in the pivotal Study ACP-2566-003 and both RTTDB and RTTLT Pools.

In the RTTDB Pool, the incidence of TEAEs of vomiting was 19.9% (35 of 176 subjects) in the All Trofinetide group and 9.0% (12 of 133 subjects) in the Placebo group. The incidence of vomiting appeared to decrease with older age. There were no serious TEAEs of vomiting in either the All Trofinetide or Placebo group.

TEAEs of vomiting considered by the Investigator to be related to study drug occurred in 18 (10.2%) subjects in the All Trofinetide group and 2 (1.5%) subjects in the Placebo group.

The majority of TEAEs of vomiting were mild or moderate in severity, with only 1 (0.6%) subject in the All Trofinetide group experiencing severe vomiting. None of the TEAEs of vomiting were fatal.

The mean onset of vomiting was 19.8 days in the trofinetide group vs. 26.9 days in the placebo group in the pivotal Study ACP-2566-003 (within the RTTDB Pool), and the mean duration was 26.3 days in the trofinetide group vs. 3.3 days in the placebo group.

Two (1.1%) subjects in the All Trofinetide group had TEAEs of vomiting that led to study discontinuation. No subjects in the Placebo group discontinued due to vomiting.

In the RTTLT Pool, the incidence of TEAEs of vomiting was 37.1% (66 of 178 subjects) in trofinetide-treated subjects, it was comparable among subjects with <6 weeks of treatment (22.5%) compared with subjects treated for ≥6 weeks (21.9%). Two (1.1%) subjects had a serious TEAE of vomiting.

TEAEs of vomiting considered by the Investigator to be related to study drug occurred in 34 (19.1%) subjects.

The majority of TEAEs of vomiting were mild or moderate in severity, with 2 (1.1%) subjects experiencing severe vomiting. One (0.6%) subject had a fatal TEAE of vomiting. The cause of death was determined to be vomiting leading to aspiration, and aspiration of gastrointestinal contents into the airways. The TEAE of vomiting in this subject was not considered related to study drug by the Investigator.

Twelve (6.7%) subjects had TEAEs of vomiting that led to study discontinuation.

Vomiting may have a significant impact on the patients receiving trofinetide, increasing the risk of dehydration or possibly lead to secondary risk of aspiration or aspiration pneumonia, requiring dose reduction, interruption or treatment discontinuation.

In the RTTDB Pool, no subjects experienced aspiration in either of the treatment groups. Two (1.1%) subjects experienced pneumonia aspiration in the All Trofinetide group and none in the Placebo group. Neither of the events were serious or severe.

In the RTTLT Pool, there were 2 serious events of aspiration in 1 subject within <6 weeks and in 1 within ≥6 weeks from the first dose of trofinetide. Five subjects (2.8%) experienced pneumonia aspiration, of which 1 (0.6%) was considered serious. All TEAEs occurred ≥6 weeks from the first dose of trofinetide.

One subject in Study ACP-2566-005 (RTTLT Pool) experienced a fatal aspiration following G-tube placement. The cause of death was vomiting leading to aspiration, and aspiration of gastrointestinal contents into the airways. It was recorded as a serious TEAE and not related to trofinetide.

Three cases of aspiration pneumonia with vomiting (serious) were reported in the post-marketing period of 10 June 2023 to 09 September 2023. Two cases of aspiration and 5 cases of aspiration pneumonia (all serious) were reported in the post-marketing period of 10 September 2023 to 09 December 2023, out of 7 reports, 2 were assessed as related, the rest

of 5 reports as un-related. During the post-marketing period of 10 December 2023 to 09 March 2024, 4 reports of aspiration and 7 reports of aspiration pneumonia were received (all serious). No reports of aspiration and 10 reports of aspiration pneumonia were reported in the post-marketing period of 10 March 2024 to 09 June 2024. All were serious and all but one were assessed by the MAH as not related to trofinetide. Two of the reports were associated with vomiting. During the post-marketing period of 10 June 2024 to 09 September 2024, one report of aspiration and 4 reports of aspiration pneumonia were received. All were serious and none were assessed by the MAH as related to trofinetide. Two of the aspiration pneumonia reports were associated with vomiting.

RTT is characterised by serious pathophysiology, including breathing and feeding dysfunctions, and alteration of cardiorespiratory coupling, a consequence of multiple interrelated disturbances in the genetic and homeostatic regulation of central and peripheral neuronal networks, redox state, and control of inflammation (Ramirez et al. 2020). The incidence of recurrent aspiration in selected groups of individuals with intellectual or developmental disability has shown aspiration at 26 and 27%, respectively. In addition, individuals with RTT present many factors that may interrupt smooth eating and swallowing, such as apraxia, ataxia, and breathing abnormalities. These incidents are apparent especially during waking hours and as they interfere with the complex mechanism of eating, they may cause recurrent aspirations (Lotan and Zysman 2006).

RTT patients exhibit poor coordination between breathing and chewing, which results in increased air in the pharyngeal space that is swallowed with the bolus and aspiration of foreign material into the lungs.

The adverse effect of vomiting with trofinetide may increase the risk of aspiration.

As per Ramirez et al. (2020), it is not clear whether pneumonia is the result of predisposition to lung conditions or due to orally ingested versus secretion-related aspirations. Dyscoordination with swallowing may contribute to pneumonia (Ramirez et al. 2022). *Mecp2*-null mouse model reported by Kida et al. (2017) suggested that the expression of inflammatory response genes is associated with the pathology of aspiration pneumonia in *Mecp2*-null mice. Aspiration of vomit may result in aspiration pneumonitis (due to low pH), and result in conditions favourable for infectious pneumonia to develop.

As per the International Rett Syndrome Foundation, thickeners for liquids may be helpful to prevent aspiration and need for a G-tube.

According to Ramirez et al. (2020), the mechanisms leading to dysphagia in RTT patients are poorly understood. Swallowing is a complex behaviour, requiring the coordination of muscles and cranial nerves and is accomplished in three distinct phases: oral, pharyngeal, and oesophageal. According to the authors, the few studies that evaluated dysphagia in RTT suggest that several factors impair this first (oral) phase. RTT patients have several issues that affect this first (oral) phase, including malocclusion (open bite), difficulty chewing, poor tongue mobility, involuntary movements of the tongue, poor bolus formation, and poor glossopharyngeal seal. All these factors lead to complications in the subsequent pharyngeal

phase of swallow, which include pharyngeal spill, pharyngeal delay, and impaired oropharyngeal clearance, resulting in potential aspiration (Ramirez et al. 2020).

– Patients with RTT often do have oral intake impairments and require G-tubes. Aspiration, aspiration pneumonia and co-occurring morbidities are not uncommon as are other infectious complications that can arise from a relatively immobile dependent state. Because aspiration and aspiration pneumonia are known effect of RTT, aspiration and the cases reported were not considered drug related. Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

    - Diarrhoea

Diarrhoea was the most commonly reported TEAE in the pivotal Study ACP-2566-003 and both RTTDB and RTTLT Pools.

In the RTTDB Pool, the incidence of TEAEs of diarrhoea was 56.8% (100 of 176 subjects) in the All Trofinetide group and 16.5% (22 of 133 subjects) in the Placebo group. The incidence of TEAEs of diarrhoea was higher among subjects treated with trofinetide ≥200 to 500 mg/kg twice daily (BID) (76.5%) compared with subjects treated with trofinetide <200 mg/kg BID (20.9%). No subject had a serious TEAE of diarrhoea.

TEAEs of diarrhoea considered by the Investigator to be related to study drug occurred in 84 (47.7%) subjects in the All Trofinetide group and 12 (9.0%) subjects in the Placebo group.

The majority (98.9%) of TEAEs of diarrhoea were mild or moderate in severity, with only 3 (1.7%) subjects in the All Trofinetide group experiencing severe diarrhoea. None of the TEAEs of diarrhoea were fatal.

The mean onset of diarrhoea was 6.5 days in the trofinetide group vs. 15.9 days in the placebo group in the pivotal Study ACP-2566-003 (within the RTTDB Pool), and the mean duration was 51.4 days in the trofinetide group vs. 16.4 days in the placebo group.

Thirteen (7.4%) subjects in the All Trofinetide group had TEAEs of diarrhoea that led to study discontinuation. No subjects in the Placebo group discontinued due to diarrhoea.

In the RTTLT Pool, the incidence of TEAEs of diarrhoea was 85.4% (152 of 178 subjects) in trofinetide-treated subjects. The incidence was higher among subjects with <6 weeks of treatment (80.3%) compared with subjects treated for ≥6 weeks (30.2%), supporting favourable long-term tolerability. No subject had a serious TEAE of diarrhoea.

TEAEs of diarrhoea considered by the Investigator to be related to study drug occurred in 149 (83.7%) subjects.

The majority of TEAEs of diarrhoea were mild or moderate in severity, with only 6 (3.4%) subjects experiencing severe diarrhoea. None of the TEAEs of diarrhoea were fatal.

Forty-six (25.8%) subjects had TEAEs of diarrhoea that led to study discontinuation. The significant majority of TEAEs of diarrhoea were not associated with other morbidities, such as weight loss or dehydration, as shown by the very small number of subjects with concurrent adverse events of weight loss or dehydration in Studies ACP-2566-003, ACP-2566-004, and ACP-2566-005.

A diarrhoea management plan was offered to study sites during Studies ACP-2566-003, ACP-2566-004, and ACP-2566-005, and at the beginning of Study ACP-2566-009 including approaches such as discontinuation of ongoing constipation medication and use of loperamide and psyllium to treat the diarrhoea.

Most TEAEs of diarrhoea resolved. Anti-propulsive medications (loperamide hydrochloride, loperamide, and loperamide hydrochloride plus simethicone) were used at some point in the pivotal Study ACP-2566-003 in 3.2% of subjects in the Placebo group vs. 50.5% of subjects in the Trofinetide group. In the RTTLT Pool, around two third (64.6%) of the subjects used anti-propulsives (loperamide hydrochloride, loperamide, or loperamide hydrochloride plus simethicone) as concomitant medications to treat diarrhoea.

Despite the high frequency, the TEAEs of diarrhoea were manageable with concomitant medications, appeared to resolve, and the completion rate for subjects in the Trofinetide group was high.

- Weight loss

In the RTTDB Pool, changes in body weight to the overall postbaseline minimum and maximum values were similar among the All Trofinetide and Placebo groups. At the overall postbaseline, there was a higher percentage of subjects with ≥7% decrease in weight in the All Trofinetide than in the Placebo group (10.2% vs. 4.0%), and the results were similar in the pivotal Study ACP-2566-003 (12.9% vs. 4.7%).

The incidence of TEAEs of weight decreased was 1.7% (3 of 176 subjects) in the All Trofinetide group and 0% (none) in the Placebo group. The incidence of TEAEs of weight decreased was higher among subjects treated with trofinetide ≥200 to 500 mg/kg BID (2.6%) compared with subjects treated with trofinetide <200 mg/kg BID (0%). There were no serious TEAEs of weight decreased in either the All Trofinetide or Placebo treatment group.

TEAEs of weight decreased considered by the Investigator to be related to study drug occurred in 2 (1.1%) subjects in the All Trofinetide group. None of the TEAEs of weight decreased were severe.

One (0.6%) subject in the All Trofinetide group had a TEAEs of weight decreased that led to study discontinuation. No subjects in the Placebo group discontinued due to TEAEs of weight decreased.

In the RTTLT Pool, the percentage of trofinetide-treated subjects with potentially clinically important changes in body weight was numerically higher (22.4%) than in the RTTDB Pool. The incidence of TEAEs of weight decreased was 7.9% (14 of 178 subjects) in trofinetide-treated subjects, and it was comparable among subjects with <6 weeks of treatment (3.4%)

compared with subjects treated for ≥6 weeks (5.3%). No subject had a serious TEAE of weight loss.

TEAEs of weight decreased considered by the Investigator to be related to study drug occurred in 7 (3.9%) subjects. None of the TEAEs of weight decreased were severe. Four (2.2%) subjects had a TEAE of weight decreased that led to study discontinuation.

Patients with RTT experience weight loss and nutritional problems (Motil et al. 2012). In a large survey to determine the prevalence of common gastrointestinal and nutritional disorders in RTT based on parental reporting, feeding problems were reported in 81% of participants. Feeding problems included chewing difficulty (56%), swallowing difficulty (43%), prolonged feeding time (30 to 60 minutes; 62%), and choking or gagging with meals. Nutritional problems were reported in 47% participants, including poor weight gain/underweight (38%) and overweight (9%). In addition, in a study of participants with classic RTT and atypical RTT through the multicentre RTT Natural History, by 18 years of age, 71% of participants with classic RTT were below the second percentile on the normative reference and when participants were examined individually, 80% fell below the second percentile for weight at some point during development (Tarquinio et al. 2012).

- Decreased appetite

In the RTTDB Pool, the incidence of TEAEs of decreased appetite was 4.0% (7 of 176 subjects) in the All Trofinetide group and 2.3% (3 of 133 subjects) in the Placebo group. The incidence of TEAEs of decreased appetite was higher among subjects treated with trofinetide ≥200 to 500 mg/kg twice daily (BID) (4.3%) compared with subjects treated with trofinetide <200 mg/kg BID (3.0%). No subject had a serious TEAE of decreased appetite.

TEAEs of decreased appetite considered by the Investigator to be related to study drug occurred in 5 (2.8%) subjects in the All Trofinetide group and 2 (1.5%) subjects in the Placebo group.

All of the TEAEs of decreased appetite were mild or moderate in severity, with no subjects in the All Trofinetide group experiencing severe decreased appetite. None of the TEAEs of decreased appetite were fatal.

Three (1.7%) subjects in the All Trofinetide group had TEAEs of decreased appetite that led to study discontinuation. No subjects in the Placebo group discontinued due to decreased appetite.

In the RTTLT Pool, the incidence of TEAEs of decreased appetite was 10.1% (18 of 178 subjects) in trofinetide-treated subjects. The incidence was similar among subjects with <6 weeks of treatment (5.1%) compared with subjects treated for ≥6 weeks (5.9%). No subject had a serious TEAE of decreased appetite.

TEAEs of decreased appetite considered by the Investigator to be related to study drug occurred in 13 (7.3%) subjects.

All of the TEAEs of decreased appetite were mild or moderate in severity, with no subjects experiencing severe decreased appetite. None of the TEAEs of decreased appetite were fatal.

Four (2.2%) subjects had TEAEs of decreased appetite that led to study discontinuation.

Overall, the TEAEs of decreased appetite were not severe and manageable with a high completion rate for subjects in the Trofinetide group.

- Irritability

In the RTTDB Pool, the incidence of TEAEs of irritability was 6.8% (12 of 176 subjects) in the All Trofinetide group and 2.3% (3 of 133 subjects) in the Placebo group. The incidence of TEAEs of irritability was slightly lower among subjects treated with trofinetide ≥200 to 500 mg/kg twice daily (BID) (6.1%) compared with subjects treated with trofinetide <200 mg/kg BID (7.5%). No subject had a serious TEAE of irritability.

TEAEs of irritability considered by the Investigator to be related to study drug occurred in 5 (2.8%) subjects in the All Trofinetide group and 1 (0.8%) subjects in the Placebo group.

The majority of TEAEs of irritability were mild or moderate in severity, with 1 (0.6%) subject in the All Trofinetide group experiencing severe irritability. None of the TEAEs of irritability were fatal.

No subjects discontinued due to irritability.

In the RTTLT Pool, the incidence of TEAEs of irritability was 7.9% (14 of 178 subjects) in trofinetide-treated subjects. The incidence was lower among subjects with <6 weeks of treatment (3.4%) compared with subjects treated for ≥6 weeks (5.3%). No subject had a serious TEAE of irritability.

TEAEs of irritability considered by the Investigator to be related to study drug occurred in 9 (5.1%) subjects.

The majority of the TEAEs of irritability were mild or moderate in severity, with 1 (0.6%) subject experiencing severe irritability. None of the TEAEs of irritability were fatal.

No subjects had TEAEs of irritability that led to study discontinuation.

Overall, the TEAEs of irritability were not severe and manageable with a high completion rate for subjects in the Trofinetide group.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk(s):

None.

Important Potential Risk(s):

None.

Missing Information:

None.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of Missing Information

Not applicable.

PART II: Module SVIII - Summary of Safety Concerns

Table 15: Summary of Safety Concerns for DAYBU

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

III.2 Additional Pharmacovigilance Activities

None.

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

PART V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 16: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table 17: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not applicable

PART VI: Summary of the Risk Management Plan

Summary of risk management plan for Daybu (Trofinetide)

This is a summary of the risk management plan (RMP) for Daybu. The RMP details important risks of Daybu, how these risks can be minimised, and how more information will be obtained about Daybu's risks and uncertainties (missing information).

The summary of product characteristics (SmPC) for Daybu and its package leaflet give essential information to healthcare professionals and patients on how Daybu should be used.

This summary of the RMP for Daybu should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Daybu's RMP.

I. The medicine and what it is used for

Daybu is authorised for the treatment of neurobehavioural symptoms of Rett syndrome in adults and paediatric patients aged 5 years and older (see SmPC for the full indication). It contains trofinetide as the active substance and it is given by the oral route.

Further information about the evaluation of Daybu's benefits can be found in Daybu's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Daybu, together with measures to minimise such risks and the proposed studies for learning more about Daybu's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine *risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Daybu is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Daybu are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Daybu. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Daybu.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Daybu.

PART VII: Annexes

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

None.

Annex 6 - Details of Proposed Additional Risk Minimisation Measures

None.

Annex 7 - Other Supporting Data (Including Referenced Material)

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