

Medicines & Healthcare products Regulatory Agency

> MHRA 10 South Colonnade Canary Wharf London E14 4PU United Kingdom

gov.uk/mhra

Decision Cover Letter

Decision of the licensing authority to:

accept changes to the agreed paediatric investigation plan and to the deferral

MHRA-100046-PIP01-21-M01

Scope of the Application

Active Substance(s)

cenobamate; cenobamate

Condition(s)

Treatment of epilepsy

Pharmaceutical Form(s)

Film-coated tablet, Tablet, Oral suspension, Solution for injection

Route(s) of Administration

Oral use; Parenteral use; Gastric use;

Name / Corporate name of the PIP applicant

Arvelle Therapeutics Netherlands B.V.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Arvelle Therapeutics Netherlands B.V. submitted to the licensing authority on 22/02/2021 20:29 GMT an application for a Modification

The procedure started on 18/03/2021 10:45 GMT

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept changes to the agreed paediatric investigation plan and to the deferral

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.



Medicines & Healthcare products Regulatory Agency

> MHRA 10 South Colonnade Canary Wharf London E14 4PU United Kingdom

gov.uk/mhra

Final Decision Letter

MHRA-100046-PIP01-21-M01

Of 19/03/2021 13:01 GMT

On the adopted decision for cenobamate (MHRA-100046-PIP01-21-M01) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for cenobamate, Film-coated tablet, Tablet, Oral suspension, Solution for injection, Oral use, Parenteral use.

This decision is addressed to Arvelle Therapeutics Netherlands B.V., Johannes Vermeerplein 9, Amsterdam, Netherlands, 1071DV

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of epilepsy

2.2 Indication(s) targeted by the PIP:

Treatment of epilepsy

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

The paediatric population from birth to less than 18 years

2.4 Pharmaceutical Form(s):

Film-coated tablet; Tablet; Oral suspension; Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	2	Study 1: Development of an oral liquid suspension with minimum loading of 10 mg/ml. (CMC0X1) Study 2: Development of parenteral formulation with appropriate dose load, volume, dispensing accuracy and excipients that are suitable for the neonate population. (CMC0X2)
Non-Clinical Studies	1	Study 3: Local tolerance test: local tolerance related to intravascular and perivascular administration of the parenteral formulation (NCOX1)
Clinical Studies	7	Study 4 Open-label study to evaluate pharmacokinetics, safety and exploratory efficacy of cenobamate as adjunctive therapy in the paediatric population from 2 to less than 18 years of age with epilepsy with focal onset seizures. (COX1) Study 5 Open- label study to evaluate pharmacokinetics, safety and exploratory efficacy of cenobamate as adjunctive therapy in the paediatric population from 1 month to less than 2 years of age with epilepsy with focal onset seizures. (COX2) Study 6 Randomised, double-blind, placebo- controlled study to evaluate the efficacy, safety, and tolerability of cenobamate as adjunctive therapy in the paediatric population from 1 month to less than 4 years of age with

Extrapolation, Modeling & Simulation5Extrapolation, Modeling & Simulation5Study 10 Pork Study 10 Porks Study			
Study 7 Open-label study to evaluate pharmacokinetics, safety and efficacy of conobamate in the pacdiatric population from 2 years to less than 18 years of age with a range of pacdiatric epilepsy syndromes with generalized seizures. (COX5) Study 8 Anadomised, double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified subject study 10 evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified (QOX5, ICOX6) Study 9 9 Study to evaluate the paediatric population from 1 month to less than 18 years of age with a specified (QOX6) Study 00 evaluate pharmacokinetics (Gobel-blind phase), of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study 10 covaluate study 10 confirm or modify the paediatric population that completed studies (COX8, Study 10 Long- term open-label study 10 covaliance in the paediatric population that completed studies (COX8) Study 10 Long- term open-label study 10 covaliance in the paediatric population that completed studies (COX8) Study 10 Long- term open-label study 10 covaliance in the paediatric population that completed studies (COX8) Study 10 paper term or modify the paediatric population that completed studies (COX1, COX2, COX3, COX3, COX5, COX6 and COX8 study 10 covaliance astery of compared to the regimen used in study COX1, PopPK study to predict initial paediatric posology compared to the regimen used in study cox2, PopPK study to predict initial paediatric posology compared to the <th></th> <th></th> <th></th>			
study to evaluate pharmacokinetics, safety and efficacy of cenobamate in the 			
pharmacokinetics, safety and efficacy of cenobamate in the paediatric population from 2 years to less than 18 years of age with a range of paediatric epilepsy syndromes with generalized seizures. (COX5) Study 8 Randomised, double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5, (COX6) Study 8 Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from 5tudy 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from 5tudy 10 CoX5, COX5			
safety and efficacy of cenobamate in the paediatric oppulation from 2 years to less than 18 years of age with a range of paediatric epilepsy syndromes with generalized seizures. (COX5) Study 8 Randomised, double-bind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric oppulation from 1 works and 18 years of age with a specified epilepsy syndrome to evaluate the efficacy and safety of cenobamate in the paediatric oppulation from 1 month to less than 18 years of age with a specified epilepsy syndrome to evaluate the efficacy and safety of cenobamate in the paediatric oppulation from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 10 valuate pharmacokinetics (open-label phase), safety and efficacy (double-bind phase) of cenobamate in the paediatric oppulation from birth to less than 1 month of age with epilepsy with refractory scizures (COX8) Study 10 Long- term open-label study to evaluate safety of cemohamate in the paediatric oppulation that completed study to evaluate safety of cemohamate in the paediatric oppulation that completed study to contin or modify the paediatric population that completed study to contin or modify the paediatric oppulation does to be used in study 12 PopPK study to contin or modify the paediatric does to be wediatric does to be study to predict initial paediatric does to be study to predict initial <br< th=""><th></th><th></th><th></th></br<>			
of cinobamate in the paediatric population from 2 years to less than 18 years of paediatric epilepsy syndromes with generalized seizures. (COX5) Study 8 Randomised, double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome a subject of the second study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 10 evaluate pharmacokinetics (open-label phase), safety and efficacy of cenobamate in the paediatric population from birth to less that 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less (COX1, COX2, COX3, COX5, COX6, and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric poperK study to confirm or modify the paediatric does to be used in study cox12 PopPK study to confirm or modify the paediatic popology compared to the regimen used in study COX1, COX2, PopPK study to predict initial paediatic does to be used in study cox2, PopPK study to predict initial paediatic does to be used in study to predict initial paediatic does to be			
Packaticpackiatricpopulation from 2: years to less than 18 years of age with a range of packiatric epilepsy syndromes with generalized seizures. (COX5) Study 8 Randomised, double-bind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the pacediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5, (COX6) Study 9 Study 10 evaluate the efficacy and safety of cenobamate in the pacediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5, (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-bind phase) (double-bind phase) (double-bind phase)safety and efficacy (double-bind phase) from birth to less than 1 month of age that norm offy the representation phase) control equilation from birth to less that 1 month of age that 10 paceliatric population that completed study to evaluate safety of centobarate in the pacediatric population that completed study to confirm or modify the pacediatric population that completed study to confirm or modify the pacediatric population that completed study to confirm or modify the pacediatric does to be used in study 12 PopPK study to confirm or modify the pacediatric does to confirm or modify the pacediatric population poology compared to the regimen used in study COX1. PopPK study to confirm or modify the pacediatric does to be used in study to predict initial pacediatric does to be used in study to predict initial pacediatric does to be used in study to predict initial pacediatric does to be used in			
from 2 years to less than 18 years of age with a range of padiatric epilepsy syndromes with generalized scizures. (COX5) Study 8 Randomised. double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric oppulation from 1 month to less than 18 years of age with a specified epilepsy syndrome a determined by the results from Study 2008 Study 9 Study to evaluate the results from Study COX5. (COX6) Study 9 Study to evaluate the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy of cenobamate in the paediatric oppulation from birth to less than 1 hours of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less. (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less. (COX1) COX2. COX3. (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric population from birth or hord cox1. PopPK study to constart to the regimen used in study COX1. PopPK study to confirm or modify the paediatric population from birthy the confirm or modify the paediatric population from birthy the paediatric poper conpared to the regimen used in study COX2. PopPK study to confirm or modify the paediatric population from birthy the paediatric <b< th=""><th></th><th></th><th></th></b<>			
Extrapolation, Modeling & Simulation5Study 11 PopPK sudyStudies of the studyStudy 22, PopPKStudy 32, COX3Study 34, CoxeliantStudy 34, CoxeliantStudiesStudiesStudy 34, Study 34, St			
Extrapolation, Modeling & Simulation 5 Extrapolation, Modeling & Simulation 5 Study 11 PopPK study 10 Study 22, COX3 11 Studies 5			
Extrapolation, Modeling & Simulation5Extrapolation, Modeling & Simulation55<			
with generalized seizures. (COX5)Study 8 Randomised, double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study (COX5, (COX6) Study 9 Study to evaluate that a specified epilepsy syndrome as determined by the results from Study (COX5, (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric popolation that completed study to confirm or modify the paediatric popolation studies COX1, PopPK study to 2009/COX1, PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1, PopPK study to 2009/COX1, PopPK study to 2009/COX2, PopPK study to 2009/COX2, PopPK study to predict initial paediatric posology compared to the regimen used in study study to 2007/COX2, PopPK study to 2007/COX2, PopPK study to 2007/COX2, PopPK study to 2007/COX2, PopPK study to 2007/COX2, PopFK			
seizures. (COS5)Study 8 Randomised. double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate the phase), safety and efficacy of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate that and efficacy (double-blind phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6, COX6 and COX8 StudiesExtrapolation, Modeling & Simulation Studies5Studies5Studies5Studies (OX1, PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1, PopPK study to confirm or modify the paediatric doses to be used in study concilic initial paediatric posology compared to the regimen used in study COX2, PopPK study to predict initial paediatric doses to be to the regimen used in study concilic initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric doses to be be			
Study 8 Randomised, double-blind, placebo- controlled study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epileps syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from bit to less than 1 month of age with epileps with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1. COX2, COX3, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to coX2 and COX8 (MS1) Study 12 PopPK study to predict initial paediatric posology compared to the regimen used in study COX1. PopFK study to predict initial paediatric posology compared to the regimen used in study coX2 and COX2 and COX8 (MS1) Study 12 PopPK study to predict initial paediatric posology compared to the regimen used in study coX2 and COX2 and COX2 and COX8 and the regimen used in study coX2 and propic initial paediatric posology compared to the regimen used in study coX2 and POXPK study to predict initial paediatric posology compared to the regimen used in study coX2 and POXPK study to predict initial paediatric posology compared to the regimen used in study coX2 and POXPK study to the regimen used in study coX2 and POXPK study to the regimen used in study coX2 a			
double-billed study to evaluate the efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COXS. (COXS) Study 9 Study to evaluate pharmacokinetics (double-billing phase), safety and efficacy (double-billing phase), of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- (COX8) Study 10 Long- (COX8) Study 10 Long- (COX8) Study 10 Long- (COX8) Study 10 Long- (COX9) Study 10 Long-			
Extrapolation, Modeling & Simulation5Studies5Study is Simulation5Study 12 PopPK study to confirm or modify the paediatric poslogy compared to the regimen used in study cOX1. 2028 and cOX8			
to evaluate he' efficacy and safety of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), of cenobamate in the paediatric population from birth or less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX3, COX5, COX6 and COX8 (COX5, COX6 and COX8 (COX1) PopPK study to confirm or modify the paediatric pooled study to PopPK study to predict initial paediatric does to be used in study 12 PopPK study to 2005 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study cOX1. PopPK study to predict initial paediatric does to be used in study cox2. PopPK study to PopK study to predict initial paediatric posology compared to the regimen used in study to PopK study to			
Extrapolation, Modeling & Simulation5Study 11 PopPK study to regimen used in study COX1, COX2, COX3, COX5, COX6, COX6, Study 12 Pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than it hepipesy with refactory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less than it month of age with refactory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less than i the paediatric population that completed studies COX1, COX2, COX3, COX8, SCOX8, S			
of cenobamate in the paediatric population from 1 month to less than 18 years of age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to completed studies COX5, COX6 and COX8, Study to evaluate study to evaluate of cenobamate in the paediatric population from bit to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to completed studies COX1, COX2, COX3, COX5, COX6 and COX8, Study 11 PopPK study to predict initial paediatric doesd in study COX1. PopPK study to predict initial paediatric doesd in study COX1. PopPK study to orredict initial paediatric doesd in study COX1. PopPK study to orredict initial paediatric doesd in study confirm or modify the paediatric popeK study to confirm or modify the paediatric posediatic to popRK study to predict initial paediatric to posediation to confirm or modify the paediatric posediatic to popRK study to predict initial paediatric to posediatic to posediatic to popRK study to predict initial paediatic to posediatic to posediatic to posediatic to popRK study to predict initial paediatic to posediatic to pose to be to perfice tinitial paediatic to pose to be to popRK study to predict initial paediatic to pose to be the paediatic to pose to be to paediatic to pose to be to paediatic to pose to be to predict initial pa			
Extrapolation, Modeling & Simulation5Suddial5Study 10 perform compared to the regiment of the <th></th> <th></th> <th></th>			
Form 1 month to less than 18 years of age with a specified epilepsy syndrome 			
Extrapolation, Modeling & Simulation5Study 10 PoPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric popR study to be used in study 10 PoPK study to predict initial paediatric popR study to predict initial paediatric popR study to paediatric popR study to predict initial paediatric popR study to confirm or modify the paediatric popR study to predict initial paediatric popR study to predict initial paediatric popR study to predict initial paediatric posology compared to the predict initial paediatric posology compared to the posology compared to the predict initial paediatric posology compared to the posology compared to the predict initial paediatric posolog			
age with a specified epilepsy syndrome as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population from birth to less (that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX8)Extrapolation, Modeling & Simulation5Studies5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology confirmed to the regimen used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be			
epilepsy syndrome as determined by the results from Study COX5, (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase), safety and efficacy substance (double-blind phase), safety and efficacy (double-blind phase), safety and efficacy substance (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9) 9Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1, PopPK study to predict initial paediatric doses to be used in study COX2, and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX2, PopPK study to predict initial paediatric posology compared to the regimen used in study COX2, PopPK study to predict initial paediatric posology compared to the regimen used in study COX2, PopPK study to predict initial paediatric posology compared to the regimen used in study COX2, PopPK study to predict initial paediatric doses to be be doses to be be doses to be be doses to be be doses to be doses			
as determined by the results from Study COX5. (COX6) Study 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1, PopPK study to enditaric posology compared to studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study confirm or modify the paediatric posology compared to the regimen used in study confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be used in to the to be used in to the regimen used in study to predict initial paediatric doses to be used in to the regimen used in to the to be used in to the regimen used in to the			
Extrapolation, Modeling & Simulation5Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long-term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric poso			
Extrapolation, Modeling & Simulation5COX5. (C0X6) Sindy 9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to operation studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be used in study compared prediction to study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study compared predictinitial paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study compared predictinitial paediatric doses to be be to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be be to be be to be be to be be to be be to be be to be to be be to be be to be be to be be to be to be be to be 			
9 Study to evaluate pharmacokinetics (open-label phase), safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be			
ComparisonSinulationStudies5Studies <t< th=""><th></th><th></th><th></th></t<>			
safety and efficacy (double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies (COX9)Extrapolation, Modeling & Simulation5Studies5Study 11 PopPK study to confirm or modify the paediatric poslogy compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in study confirm or modify the paediatric poslogy compared to the regimen used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric poslogy compared to the regimen used in study to confirm or modify the paediatric doses to be to the regimen used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be			pharmacokinetics
(double-blind phase) of cenobamate in the paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Studies5Studies5Studies5Studies5Studies5Studies5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in study COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study cox2. PopPK study to predict initial paediatric doses to be used in study cox1.			(open-label phase),
extrapolation, Modeling & Simulation5Studies6Studies6Studies7Studie			
paediatric population from birth to less than 1 month of age with epilepsy with refractory seizures (C0X8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies C0X1, C0X2, C0X3, C0X5, C0X6 and C0X8 (C0X9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies			
from birth to less than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2. PopPK study to predict initial paediatric doses to be used in study coX2. PopPK study to predict initial paediatric doses to be used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be			
than 1 month of age with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Studies5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doese to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2. PopPK study to predict initial paediatric doese to be			
with epilepsy with refractory seizures (COX8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study cOX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric doses to be used in studies confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be used in study to predict initial paediatric doses to be to the regimen used in study to predict initial paediatric doses to be used in study to predict initial paediatric doses to be			
refractory seizures (C0X8) Study 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies C0X1, C0X2, C0X3, C0X5, C0X6 and C0X8 (C0X9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be to be to be used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be			
(C0X8) Študy 10 Long- term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies C0X1, C0X2, C0X3, C0X5, C0X6 and C0X8 (C0X9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study coX2. PopPK study to confirm or modify the paediatric doses to be used in study coX2. PopPK			
term open-label study to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or the paediatric posology compared to the regimen used in study to confirm or the paediatric posology compared to the regimen used in study to confirm or the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to predict initial paediatric doses to be used in study to confirm or the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be			
to evaluate safety of cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study COX1. Study 12 PopPK study to confirm or modify the paediatric doses to be used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5cenobamate in the paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2 and COX5 (MS1) Study 12 PopPK study to predict initial paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be used in study confirm or modify the paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be			
paediatric population that completed studies COX1, COX2, COX3, COX5, COX6 and COX8 (COX9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study coX2. PopPK study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to to the regimen used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study study to predict initial paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study coX2. PopPK study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5C0X1, C0X2, C0X3, C0X5, C0X6 and C0X8 (C0X9)Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study c0X2. PopPK study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study cox2. PopPK study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to predict initial paediatric doses to be to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be			
Extrapolation, Modeling & Simulation5Study 11 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study to confirm or modify the paediatric posology compared to the regimen used in study coX2. PopPK study to predict initial paediatric doses to be			
Studies to confirm or modify the paediatric posology compared to the regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be	Extrapolation, Modeling & Simulation	5	
the paediatric posology compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be		-	
compared to the regimen used in study C0X1. PopPK study to predict initial paediatric doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
regimen used in study COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be			
COX1. PopPK study to predict initial paediatric doses to be used in studies COX2 and COX5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study COX2. PopPK study to predict initial paediatric doses to be			regimen used in study
doses to be used in studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
studies C0X2 and C0X5 (MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
(MS1) Study 12 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
study to confirm or modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
modify the paediatric posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
posology compared to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
to the regimen used in study C0X2. PopPK study to predict initial paediatric doses to be			
study COX2. PopPK study to predict initial paediatric doses to be			
study to predict initial paediatric doses to be			
paediatric doses to be			
	1	1	used in studies COAO

		and paediatric doses to be used in study C0X3 (MS2) Study 13 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X8 (MS4) Study 14 PopPK study to confirm or modify the paediatric posology compared to the regimen used in study C0X5 (MS5) Study 15 Extrapolation study for paediatric patients from 4 to less than 12 years of age with epilepsy with focal-onset seizures (MS3)
Other Studies	0	Not applicable
Other Measures	0	Not applicable

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric	31/10/2029
investigation plan:	
Deferral of one or more studies contained in	Yes
the paediatric investigation plan:	