Clinical trial results:
A Double-blind, Placebo-controlled Comparative Study and Open-label Extension Study to Confirm the Efficacy and Safety of E2020 in Subjects With Down Syndrome Having Regression Symptoms and Disabled Activities of Daily Living

Summary

EudraCT number	2018-003426-89
Trial protocol	Outside EU/EEA
Global end of trial date	21 April 2017

Results information

Result version number	v1 (current)
This version publication date	17 February 2019
First version publication date	17 February 2019

Trial information

Trial identification

Sponsor protocol code	E2020-J081-345

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Co., Ltd.
Sponsor organisation address	Koishikawa 4-6-10, Bunkyo-ku, Tokyo, Japan, 1128088
Public contact	Eisai Medical Information, Eisai Inc, 81 120161454, eisai-chiken_hotline@hhc.eisai.co.jp
Scientific contact	Eisai Medical Information, Eisai Inc, 81 120161454, eisai-chiken_hotline@hhc.eisai.co.jp

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate dose-response of E2020 in change of the total score of the Body Functionality Checklist (psychosomatic function questionnaire) from baseline relative to placebo in subject s with Down syndrome who have regression symptoms and disabled activities of daily living.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	12 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 43
Worldwide total number of subjects	43
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 13 investigative sites in Japan from 12 September 2013 to 21 April 2017.

Pre-assignment

Screening details:

A total of 54 subjects were enrolled in the study, of which 2 subjects were screen failures. 52 subjects started and 9 subjects discontinued the observation phase. The 43 subjects who completed the observation phase were then randomized to receive study treatment in the treatment period.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Period: Placebo

Arm description:

Subjects received E2020 matching-placebo granules, orally, once daily, for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

E2020 matching-placebo granules, orally, once daily, for 24 weeks.

Arm title	Treatment Period: E2020 3 milligram (mg)

Arm description:

Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Donepezil Hydrochloride 3 mg
Investigational medicinal product code	E2020
Other name	Aricept
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

E2020 3 mg granules, orally, once daily, for 24 weeks.

Arm title	Treatment Period: E2020 5 mg

Arm description:

Subjects received E2020 5 mg granules, orally, once daily, for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Donepezil Hydrochloride 5 mg
Investigational medicinal product code	E2020
Other name	Aricept
Pharmaceutical forms	Granules
Routes of administration	Other use

Dosage and administration details:

E2020 5 mg granules, orally, once daily, for 24 weeks.

Number of subjects in period 1	Treatment Period: Placebo	Treatment Period: E2020 3 milligram (mg)	Treatment Period: E2020 5 mg
Started	15	14	14
Completed	15	14	13
Not completed	0	0	1
Disease Progression	-	-	1

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Extension Phase: E2020 3 mg

Arm description:

Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Donepezil Hydrochloride 3 mg
Investigational medicinal product code	E2020
Other name	Aricept
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

E2020 3 mg granules, orally, once daily, for 24 weeks.

Number of subjects in period 2[1]	Extension Phase: E2020 3 mg
Started	41
Completed	36
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Unspecified	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One subject discontinued the study during transition from Treatment period to Extension Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period: Placebo
Reporting group description:	
Subjects received E2020 matching-placebo granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 3 milligram (mg)
Reporting group description:	
Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 5 mg
Reporting group description:	
Subjects received E2020 5 mg granules, orally, once daily, for 24 weeks.	

Reporting group values	Treatment Period: Placebo	Treatment Period: E2020 3 milligram (mg)	Treatment Period: E2020 5 mg
Number of subjects	15	14	14
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 28.0 15 to 32	 23.5 15 to 37	 24.5 18 to 33
Gender categorical Units: Subjects			
Female	8	8	8
Male	7	6	6
Race Units: Subjects			
Japanese	14	14	14
Unknown or Not Reported	1	0	0

Reporting group values	Total		
Number of subjects	43		
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 -		
Gender categorical Units: Subjects			
Female	24		
Male	19		
Race Units: Subjects			
Japanese	42		

Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	Treatment Period: Placebo
Reporting group description:	
Subjects received E2020 matching-placebo granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 3 milligram (mg)
Reporting group description:	
Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 5 mg
Reporting group description:	
Subjects received E2020 5 mg granules, orally, once daily, for 24 weeks.	
Reporting group title	Extension Phase: E2020 3 mg
Reporting group description:	
Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.	

Primary: Change from Week 0 (Baseline) in Total Score Using Body Functionality Checklist (Psychosomatic Function Questionnaire) at Week 24 (Last Assessment) in Treatment Period

End point title	Change from Week 0 (Baseline) in Total Score Using Body Functionality Checklist (Psychosomatic Function Questionnaire) at Week 24 (Last Assessment) in Treatment Period

End point description:

The Body Functionality Checklist is a testing method developed as an assessment scale for regression/premature aging of the intellectually disabled. The subject's functionality of each item was evaluated on a five-point scale from the viewpoint of the caregiver and a higher point (the total score [51 items] 51 range, 51-255 points) suggests better body functionality of the subject. The full analysis set (FAS) included all subjects who received the study drug for the Treatment Period after randomization and had evaluable efficacy data at 1 or more time points after administration of the study drug for the Treatment Period.

End point type	Primary

End point timeframe:

Week 0 (Baseline) and Week 24 (Last assessment) of Treatment Period

End point values	Treatment Period: Placebo	Treatment Period: E2020 3 milligram (mg)	Treatment Period: E2020 5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	14	14	
Units: score on a scale				
arithmetic mean (standard deviation)	9.8 (± 13.2)	6.6 (± 10.4)	7.7 (± 16.4)	

Statistical analyses

Statistical analysis title	Treatment Period: Placebo v Treatment Period: E202
Comparison groups	Treatment Period: Placebo v Treatment Period: E2020 3 milligram (mg)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Cox proportional hazard

Statistical analysis title	Treatment Period: Placebo v Treatment Period: E202
Comparison groups	Treatment Period: Placebo v Treatment Period: E2020 5 mg
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAE)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAE)

End point description:

The safety analysis set (SAS) included all subjects who received the study drug for the Treatment Period and had evaluable safety data at 1 or more time points after administration of the study drug for the Treatment Period.

End point type	Secondary

End point timeframe:

From date of first dose up to Follow-up period (Week 56)

End point values	Treatment Period: Placebo	Treatment Period: E2020 3 milligram (mg)	Treatment Period: E2020 5 mg	Extension Phase: E2020 3 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	14	41
Units: subjects				
TEAE	9	12	13	29
SAEs	0	0	0	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From date of first dose up to Follow-up period (Week 56)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	Treatment Period: Placebo
Reporting group description: Subjects received E2020 matching-placebo granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 3 mg
Reporting group description: Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.	
Reporting group title	Treatment Period: E2020 5 mg
Reporting group description: Subjects received E2020 5 mg granules, orally, once daily, for 24 weeks.	
Reporting group title	Extension Phase: E2020 3 mg
Reporting group description: Subjects received E2020 3 mg granules, orally, once daily, for 24 weeks.	

Serious adverse events	Treatment Period: Placebo	Treatment Period: E2020 3 mg	Treatment Period: E2020 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Retinopathy proliferative			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension Phase: E2020 3 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Retinopathy proliferative			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment Period: Placebo	Treatment Period: E2020 3 mg	Treatment Period: E2020 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 15 (60.00%)	12 / 14 (85.71%)	13 / 14 (92.86%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Upper respiratory tract inflammation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Asthma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Intentional self-injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hallucination, visual			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Mental disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Affect lability			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood potassium increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Arthropod sting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Chillblains			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Excoriation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Bradykinesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eczema eyelids			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye inflammation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	2 / 14 (14.29%)	3 / 14 (21.43%)
occurrences (all)	2	4	7
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	5
Faeces soft			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tongue disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	3 / 15 (20.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	3	0	2
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Dermatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	4 / 14 (28.57%)	7 / 14 (50.00%)
occurrences (all)	1	4	8
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Tooth abscess			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dermatophytosis of nail			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1

Non-serious adverse events	Extension Phase: E2020 3 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 41 (70.73%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	8		

Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Asthma			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Intentional self-injury			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hallucination, visual			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Initial insomnia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Mental disorder			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Affect lability			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood potassium increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Blood triglycerides increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Arthropod sting			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Chillblains			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Excoriation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Bradykinesia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Eczema eyelids			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Eye inflammation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Dental caries			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Faeces soft			

subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Tongue disorder			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cheilitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Petechiae			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		

Dermatitis subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 2		
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	 0 / 41 (0.00%) 0 1 / 41 (2.44%) 1		
Musculoskeletal and connective tissue disorders Temporomandibular joint syndrome subjects affected / exposed occurrences (all)	 0 / 41 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Hordeolum subjects affected / exposed occurrences (all) Paronychia subjects affected / exposed occurrences (all)	 10 / 41 (24.39%) 12 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0		

Tooth abscess subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0		
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Bronchitis subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Conjunctivitis bacterial subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Subcutaneous abscess subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Dermatophytosis of nail subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Impetigo subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported