Clinical trial results:
A Phase 2a, multi-center, single-blind, within-subject, placebo-controlled study to assess the pharmacodynamics of ACT-709478 in subjects with photosensitive epilepsy

Summary

EudraCT number	2017-000494-36
Trial protocol	DE FR
Global end of trial date	25 April 2018

Results information

Result version number	v2 (current)
This version publication date	07 November 2019
First version publication date	25 May 2019
Version creation reason	• Correction of full data set Change of Sponsor.

Trial information

Trial identification

Sponsor protocol code	AC-083-103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03239691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Idorsia Pharmaceuticals Ltd
Sponsor organisation address	Hegenheimermattweg 91, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com
Scientific contact	Clinical Trial Disclosure Desk, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com

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	22 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacodynamics by means of the change in intermittent photic stimulation induced photoparoxysmal response in male and female subjects with photosensitive epilepsy following single dose administration of ACT-709478.

Protection of trial subjects:

Prior to the start of the study and implementation of the amendments, Independent Ethics Committees were consulted, i.e., review panels that were responsible for ensuring the protection of the rights, safety, and well being of human subjects involved in a clinical investigation.

Background therapy:

Subjects were allowed to be on stable background treatment (i.e., no dose changes within 4 weeks prior to screening and no changes foreseen during the study) with a maximum of 2 concomitant antiepileptic drugs. During the whole study duration, they received the antiepileptic drugs according to their regular administration schedule.

Evidence for comparator: -

Actual start date of recruitment	06 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	0
Adults (18-64 years)	5

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 countries and 5 sites

Pre-assignment

Screening details:

A screening evaluation was performed within 3–28 days before first study treatment administration for male subjects and female subjects of non-childbearing potential and within 10–28 days before first study treatment administration for female subjects of childbearing potential.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

For safety reasons, this study was conducted in a single-blind fashion. The investigator and study site personnel, the monitors, and the sponsor knew on which study days placebo or ACT-709478 was administered. In contrast, the subjects remained blinded to the study treatment until study closure. The investigational treatment and its matching placebo were indistinguishable.

Arms

Arm title	ACT-709478 single-dose / placebo administration

Arm description:

Each subject was to receive both placebo and a single dose of active treatment on consecutive days. Placebo was to be administered in the morning of Day 1 and Day 3, and ACT-709478 in the morning of Day 2.

Arm type	Experimental
Investigational medicinal product name	ACT-709478
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Hard gelatin capsules for oral administration formulated at a strength of 100 mg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Matching placebo available as matching capsules for oral administration.

Number of subjects in period 1	ACT-709478 single-dose / placebo administration
Started	5
Completed	4
Not completed	1
Treatment discontinuation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	 35.6 19 to 57	 -	
Gender categorical Units: Subjects			
Female	5	5	
BMI Units: kg/m2 arithmetic mean full range (min-max)	 25.8 23.3 to 29.2	 -	

End points

End points reporting groups

Reporting group title	ACT-709478 single-dose / placebo administration

Reporting group description:

Each subject was to receive both placebo and a single dose of active treatment on consecutive days. Placebo was to be administered in the morning of Day 1 and Day 3, and ACT-709478 in the morning of Day 2.

Primary: Positive response described as complete suppression of photoparoxysmal response or a clinically relevant reduction in the standardized photosensitive range

End point title	Positive response described as complete suppression of photoparoxysmal response or a clinically relevant reduction in the standardized photosensitive range[1]

End point description:

End point type	Primary

End point timeframe:

From Day 2 to Day 10

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See version 1.

End point values	ACT-709478 single-dose / placebo administration			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Positive response				
Subject 1	0			
Subject 2	1			
Subject 3	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time (hours) to onset of positive response

End point title	Time (hours) to onset of positive response

End point description:

Defined by the first time point after ACT-709478 administration at which complete suppression of PPR or reduction in SPR ≥ 3 units compared to baseline is achieved at least at 2 consecutive time points.

End point type	Secondary

End point timeframe:

From Day 2 to Day 10

End point values	ACT-709478 single-dose / placebo administration			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
Subject 2 - Eye closure	55			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration (hours) of positive response

End point title	Duration (hours) of positive response

End point description:

Defined as the time elapsed between the time point of onset of the positive response and the last time point of the positive response after ACT-709478 administration

End point type	Secondary

End point timeframe:

From Day 2 to Day 10

End point values	ACT-709478 single-dose / placebo administration			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
Subject 2 - Eye closure	143			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum SPR reduction

End point title	Maximum SPR reduction

End point description:

Defined as the largest reduction in SPR achieved at any time point compared to baseline during the positive response after ACT-709478 administration

End point type	Secondary

End point timeframe:
From Day 2 to Day 10

End point values	ACT-709478 single-dose / placebo administration			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: SPR reduction				
Subject 2 - Eye closure	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Time (hours) to maximum SPR reduction

End point title	Time (hours) to maximum SPR reduction

End point description:

End point type	Secondary

End point timeframe:
From Day 2 to Day 10

End point values	ACT-709478 single-dose / placebo administration			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
Subject 2 - Eye closure	127			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events treatment-emergent for placebo (from placebo administration on Day 1 up to ACT-709478 administration on Day 2) and ACT-709478 (from ACT-709478 administration on Day 2 up to EOS).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	ACT-709478
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	ACT-709478	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
generalized tonic-clonic seizure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ACT-709478	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	3 / 5 (60.00%)	
Injury, poisoning and procedural complications			
Post procedural discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Disturbance in attention			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hyperaesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Myoclonus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Application site hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Feeling of body temperature change			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Catheter site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pre-existing condition improved			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			

Hyperacusis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Tension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Euphoric mood			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Initial insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2017	Amendment 1 was a substantial amendment finalized before the start of the clinical conduct of the study. This amendment was issued in response to two requests expressed by BfArM: 1) The inclusion of the submission of a protocol amendment in the procedure to continue the study, e.g., with an intermediate dose, if a stopping criterion is met for dose escalation. 2) The C-SSRS was added in order to exclude subjects with a history of suicidal thoughts or attempted suicide and to monitor the subjects for signs of suicidal thoughts or suicidal behavior during the course of the study.
28 November 2017	Amendment 2 specified the change of sponsorship of the study from Actelion Pharmaceuticals Ltd to Idorsia Pharmaceuticals Ltd, effective from 1 March 2018

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the late occurrence, the positive response in one subject was not considered relevant.

Notes: