Clinical trial results:
A prospective, multicenter study to investigate the pharmacokinetics, safety, and efficacy of cadazolid versus vancomycin in pediatric subjects with Clostridium difficile-associated diarrhea.

Summary

EudraCT number	2015-004805-17
Trial protocol	BE HU IT ES
Global end of trial date	17 April 2018

Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

Trial information

Trial identification

Sponsor protocol code	AC-061A303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03105479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.com
Scientific contact	Clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001108-PIP02-15
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	24 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Two parts were planned for this study:
- The primary objective of Part A was to determine the cadazolid dose in children from birth to < 18 years of age by investigating the safety, efficacy, and the systemic and fecal pharmacokinetics (PK).
- The primary objective of Part B was to assess the safety and efficacy of cadazolid in children from birth to < 18 years of age as compared with vancomycin.

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and with the ethical principles laid down in the Declaration of Helsinki.
The study was conducted by investigators experienced in the treatment of pediatric patients.
In Part A, children were enrolled sequentially by groups of 3 subjects, starting with 3 adolescents aged between 12 and 18. After the completion of each group of 3, enrollment was temporarily put on hold and safety, pharmacokinetics and efficacy data reviewed by an Independent Data Monitoring Committee (IDMC) before enrollment of the next 3 subjects. Part B could start only when a dosing recommendation from the corresponding age cohort was available based on Part A.

Background therapy: -

Evidence for comparator:

The comparator, vancomycin, to be used in part B, is approved in Europe and in the US for the treatment of mild–moderate CDAD

Actual start date of recruitment	13 April 2017
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	United States: 1
Worldwide total number of subjects	1
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)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Only one subject was enrolled in Part A. Part B was not conducted due to early study termination after the sponsor's decision to discontinue the clinical development program for cadazolid, taking into account the results of the two pivotal trials in adults.

Pre-assignment

Screening details:

Enrollment was to be staggered by age group starting with the older children (≥12 years). Enrollment in a younger age group was planned to initiate only following a review by the IDMC of the safety, pharmacokinetic and efficacy data from the first 3 children from the previous older age group.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cadazolid-Part A

Arm description:

The anticipated starting doses were based on weight categories.

Arm type	Experimental
Investigational medicinal product name	cadazolid
Investigational medicinal product code	ACT-179811
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Administration twice daily for 10 days

Number of subjects in period 1	Cadazolid-Part A
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period
Reporting group description:	
Part A	

Reporting group values	Overall study period	Total	
Number of subjects	1	1	
Age categorical Units: Subjects			
Adolescents (12 years to < 18 years)	1	1	
Children (2 years to< 12 years)	0	0	
Infants and toddlers (3 months to < 2 years)	0	0	
Gender categorical Units:			
Male	0	0	
Female	1	1	

End points

End points reporting groups

Reporting group title	Cadazolid-Part A

Reporting group description:

The anticipated starting doses were based on weight categories.

Primary: Maximal plasma concentration (Cmax) of cadazolid during part A

End point title	Maximal plasma concentration (Cmax) of cadazolid during part A[1]

End point description:

Blood samples were collected at different timepoints for the determination of cadazolid Cmax. Due to the premature study termination, cadazolid concentrations were obtained from only one subject and pharmacokinetic plasma profile was not analyzed because of lack of meaningful data.

End point type	Primary

End point timeframe:

Day 10 (pre-dose, and 1h, 2h, 4h and 12h post-dose)

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: Because the study was prematurely terminated with only 1 subject enrolled, no statistical analyses were performed.

End point values	Cadazolid-Part A			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: ng/mL				
geometric mean (confidence interval 95%)	(to)			

Notes:

[2] - No analysis performed due to early termination

Statistical analyses

No statistical analyses for this end point

Primary: Area under the plasma concentration curve (AUC) of cadazolid during part A

End point title	Area under the plasma concentration curve (AUC) of cadazolid during part A[3]

End point description:

Blood samples were collected at different timepoints for the determination of cadazolid AUC. Due to the premature study termination, cadazolid concentrations were obtained from only one subject and pharmacokinetic plasma profile was not analyzed because of lack of meaningful data.

End point type	Primary

End point timeframe:

Day 10 (pre-dose, and 1h, 2h, 4h and 12h post-dose)

Notes:

[3] - 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: Because only one subject was enrolled in the study and consequent lack of meaningful data, no statistical analyses were performed.

End point values	Cadazolid-Part A			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: ng*h/mL				
geometric mean (confidence interval 95%)	(to)			

Notes:

[4] - No analysis performed due to early termination

Statistical analyses

No statistical analyses for this end point

Primary: Time to reach Cmax of cadazolid during part A

End point title	Time to reach Cmax of cadazolid during part A[5]

End point description:

Blood samples were collected at different timepoints to determine the time when the maximal plasma concentration of cadazolid (Cmax) is reached. Due to the premature study termination, cadazolid concentrations were obtained from only one subject and median tmax could not be determined because of lack of meaningful data.

End point type	Primary

End point timeframe:

Day 10 (pre-dose, and 1h, 2h, 4h and 12h post-dose)

Notes:

[5] - 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: Because the study was prematurely terminated with only 1 subject enrolled, no statistical analyses were performed.

End point values	Cadazolid-Part A			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: hours				
median (full range (min-max))	(to)			

Notes:

[6] - No analysis performed due to early termination

Statistical analyses

No statistical analyses for this end point

Primary: Faecal concentrations of cadazolid during part A

End point title	Faecal concentrations of cadazolid during part A[7]

End point description:

A faecal sample was collected at the end-of-treatment visit.
Due to premature termination, faecal sample was collected from only one subject, consequently further analyses (descriptive and statistical analyses) could not be conducted.

End point type	Primary

End point timeframe:

Day 10

Notes:

[7] - 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: Because the study was prematurely terminated with only 1 subject enrolled, no statistical analyses were performed.

End point values	Cadazolid-Part A			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: mcg/g				
number (not applicable)	4520			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study treatment initiation up to Day 37 (i.e., 27 Days after the end of treatment)

Adverse event reporting additional description:

All adverse events (AE) which occurred at any time during the treatment period (10 days with cadazolid) and during the follow-up period (about 30 days) are reported.
All AEs reported below occurred during the follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Cadazolid-Part A

Reporting group description:

One adolescent received cadazolid 250 mg twice daily during 10 days

Serious adverse events	Cadazolid-Part A		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Cadazolid-Part A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

sore throat subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2016	The main reason for this amendment is to align the global protocol with the cadazolid Paediatric Investigation Plan (PIP) European Medicines Agency's (EMA) decision and to align with FDA requirements.
01 March 2017	The main reason for this amendment is to address agreed changes in the responses to Voluntary Harmonisation Procedure (VHP) list of grounds for non-acceptance, dated 10 February 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 October 2017	Enrollment suspended during strategy review.	-

Notes:

Limitations and caveats

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

Results are not meaningful because only one patient was included in this study due to early termination

Notes: