



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) | EMA-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 | 1 / 1 (100.00%) | | |
| occurrences (all) | 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: