



Clinical trial results:

A Multi-center, Randomized, Double-blind, Comparative Study to Evaluate the Safety and Efficacy of ZTI-01 Versus Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Hospitalized Adults

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2015-003372-73 |
| Trial protocol | CZ HU LT LV SK PL EE GR BG RO HR |
| Global end of trial date | 12 January 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 29 September 2018 |
| First version publication date | 29 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | ZTI-01-200 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02753946 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Zavante Therapeutics, Inc. (a Nabriva Therapeutics, plc entity) |
| Sponsor organisation address | 11750 Sorrento Valley Road, Suite 250, San Diego, CA 92121, United States, |
| Public contact | David Skarinsky, Zavante Therapeutics, Inc. (a Nabriva Therapeutics, plc entity), 001 8582994921, David.Skarinsky@nabriva.com |
| Scientific contact | Evelyn J. Ellis-Grosse, Zavante Therapeutics, Inc. (a Nabriva Therapeutics, plc entity), 001 8582994921, Evelyn.Ellis.Grosse@nabriva.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 | 31 January 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that ZTI-01 was non-inferior to Piperacillin-Tazobactam (PIP-TAZ) in overall success (clinical cure and microbiologic eradication) in the microbiologic Modified Intent-to-Treat (m-MITT) Population at the Test-of-Cure (TOC) Visit

Protection of trial subjects:

The study was conducted in full compliance with the principles of the Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, and all of the applicable United States (US) Code of Federal Regulations (CFR), 21 CFR Parts 50 & 312. Prior to the beginning of the study, the Investigator was to have the IRB/IECs' written approval of the written informed consent form and any other information to be provided to patients.

Before undertaking any study-related procedures with patients, the purpose and nature of the study, as well as possible adverse effects, were explained to the patients in understandable terms and written informed consent was obtained from each individual. Each informed consent was to be appropriately signed and dated by the patient and the person obtaining consent. Each patient was to receive a copy of the signed informed consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 21 June 2016 |
| 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 | Poland: 22 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | Slovakia: 24 |
| Country: Number of subjects enrolled | Croatia: 8 |
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Estonia: 10 |
| Country: Number of subjects enrolled | Hungary: 9 |
| Country: Number of subjects enrolled | Latvia: 29 |
| Country: Number of subjects enrolled | Lithuania: 13 |
| Country: Number of subjects enrolled | Belarus: 70 |
| Country: Number of subjects enrolled | Georgia: 25 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 78 |
| Country: Number of subjects enrolled | Ukraine: 144 |
| Country: Number of subjects enrolled | United States: 1 |
| Worldwide total number of subjects | 465 |
| EEA total number of subjects | 147 |

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) | 314 |
| From 65 to 84 years | 140 |
| 85 years and over | 11 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were performed within 48 hours prior to randomization on Day 1.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Subject, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------|
| Arm title | ZTI-01 |
|------------------|--------|

Arm description: -

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Fosfomycin for injection |
| Investigational medicinal product code | ZTI-01 |
| Other name | Disodium fosfomycin |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

6 g ZTI-01 in water for injection intravenously (IV) administered every 8 hours infused over 1 hour.

| | |
|------------------|---------|
| Arm title | PIP-TAZ |
|------------------|---------|

Arm description: -

| | |
|--|-------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Piperacillin [PIP]/Tazobactam [TAZ] |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

4.5 g PIP-TAZ (4 g PIP/0.5 g TAZ) IV administered every 8 hours infused over 1 hour.

| Number of subjects in period 1 | ZTI-01 | PIP-TAZ |
|--------------------------------|--------|---------|
| Started | 233 | 232 |
| Completed | 221 | 230 |
| Not completed | 12 | 2 |
| Consent withdrawn by subject | 8 | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 3 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------|
| Reporting group title | ZTI-01 |
| Reporting group description: - | |
| Reporting group title | PIP-TAZ |
| Reporting group description: - | |

| Reporting group values | ZTI-01 | PIP-TAZ | Total |
|---|---------|---------|-------|
| Number of subjects | 233 | 232 | 465 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 159 | 155 | 314 |
| From 65-84 years | 67 | 73 | 140 |
| 85 years and over | 7 | 4 | 11 |
| Age continuous Units: years | | | |
| arithmetic mean | 49.5 | 50.8 | |
| standard deviation | ± 20.55 | ± 20.87 | - |
| Gender categorical Units: Subjects | | | |
| Female | 151 | 146 | 297 |
| Male | 82 | 86 | 168 |

End points

End points reporting groups

| | |
|--------------------------------|---------|
| Reporting group title | ZTI-01 |
| Reporting group description: - | |
| Reporting group title | PIP-TAZ |
| Reporting group description: - | |

Primary: Proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the Test-of-Cure (TOC) Visit.

| | |
|--|--|
| End point title | Proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the Test-of-Cure (TOC) Visit. |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| The timeframe for the primary end point was the TOC Visit, that was completed on Day 19 (+2 Days). | |

| End point values | ZTI-01 | PIP-TAZ | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 184 | 178 | | |
| Units: percent | | | | |
| number (not applicable) | 64.7 | 54.5 | | |

Statistical analyses

| | |
|--|--------------------------|
| Statistical analysis title | Proportion of Responders |
| Statistical analysis description: | |
| Percentages were calculated using the number of patients in the microbiologic Modified Intent-to-Treat (m-MITT) Population as the denominator. | |
| a. Treatment difference was the difference in the overall success rate between the 2 treatment groups (ZTI-01/PIP-TAZ). | |
| The 95% confidence interval (CI) (2-sided) was computed using a continuity-corrected Z-statistic. | |
| b. Overall success was defined as clinical cure and microbiologic eradication. | |
| Comparison groups | ZTI-01 v PIP-TAZ |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (net) |
| Point estimate | 10.2 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 20.8 |
| Variability estimate | Standard error of the mean |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Day 26 (+/- 2 days; Late Follow-up Visit).

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|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | ZTI-01 |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | PIP-TAZ |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | ZTI-01 | PIP-TAZ | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 233 (2.15%) | 6 / 231 (2.60%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastatic gastric cancer | | | |
| subjects affected / exposed | 1 / 233 (0.43%) | 0 / 231 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 233 (0.00%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 233 (0.00%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 233 (0.43%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 233 (0.43%) | 0 / 231 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic abscess | | | |
| subjects affected / exposed | 1 / 233 (0.43%) | 0 / 231 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 233 (0.00%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal abscess | | | |
| subjects affected / exposed | 0 / 233 (0.00%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic embolus | | | |
| subjects affected / exposed | 0 / 233 (0.00%) | 1 / 231 (0.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 233 (0.43%) | 0 / 231 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | ZTI-01 | PIP-TAZ | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 96 / 233 (41.20%) | 73 / 231 (31.60%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 233 (8.58%) | 6 / 231 (2.60%) | |
| occurrences (all) | 22 | 11 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 17 / 233 (7.30%) | 6 / 231 (2.60%) | |
| occurrences (all) | 17 | 8 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 233 (2.58%) | 5 / 231 (2.16%) | |
| occurrences (all) | 6 | 5 | |
| General disorders and administration site conditions | | | |
| Infusion site phlebitis | | | |
| subjects affected / exposed | 2 / 233 (0.86%) | 6 / 231 (2.60%) | |
| occurrences (all) | 2 | 6 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 10 / 233 (4.29%) | 3 / 231 (1.30%) | |
| occurrences (all) | 11 | 3 | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 233 (3.86%) | 11 / 231 (4.76%) | |
| occurrences (all) | 9 | 12 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 233 (3.86%) | 1 / 231 (0.43%) | |
| occurrences (all) | 9 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 14 / 233 (6.01%) | 3 / 231 (1.30%) | |
| occurrences (all) | 15 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 03 December 2015 | <p>Amendment 1:</p> <ul style="list-style-type: none">-The study was changed from a Phase 2 study to a Phase 2/3 study.-The primary objective was changed to the demonstration that ZTI-01 is non-inferior to PIP-TAZ in overall success in the treatment of cUTI or AP, and secondary objectives were added to include the comparison of the clinical cure rates and microbiologic eradication of the 2 treatment groups.-The population for the study was increased from approximately 200 patients to 460 patients to increase the power of the study.-Elevated WBC count was eliminated as a sign or symptom of cUTI or AP.-The duration of contraception requirements for study participants was shortened based on toxicity studies.-The threshold for the thrombocytopenia exclusion criterion was lowered from 60,000 platelets/mm³ to 50,000 platelets/mm³.-The 4 g ZTI-01 treatment group was eliminated, and the ratio of patients randomized to the 2 treatment groups was changed to 1:1.-The duration of treatment was changed to 7 days for all patients unless deemed a treatment failure, and the TOC Visit was changed to Day 12 (+2 days).-A DMC was added to assess safety and evaluability during the study.-Outcome definitions were clarified.-The secondary efficacy analyses at the LFU Visit were made additional efficacy analyses to support the primary and secondary outcomes.-The statistical efficacy analyses were updated to reflect the changes in the primary and secondary objectives and efficacy analyses.-The sample size rationale was updated to reflect the increased sample size and power of the study.-The number of sites was increased from 60 to 100 to 115.-An unblinded site monitor was added to ensure the blind was maintained throughout the study.-Infusion of 5% dextrose to maintain the blind was added in situations where patients may not be safely administered free WFI.-The 12-lead ECG in triplicate was changed to a single reading.-Changes were also made for clarity and/or consistency. |

| | |
|---------------|---|
| 29 March 2016 | <p>Amendment 2:</p> <ul style="list-style-type: none"> -Changes were made to inclusion and exclusion criteria; -Procedures for dosing in patients with renal insufficiency were specified; -The duration of treatment was changed to 7 to 14 days, the TOC Visit was changed to Day 19, and the LFU Visit was changed to Day 26; -Urine isolate growth criteria was changed to $>1 \times 10^3$ CFU/mL for laboratory analysis; -Baseline urine and blood samples submitted to the central laboratory were specified; -Patient treatment in cases of non-susceptibility to study drug was provided; -Determination of serum creatinine within 24 hours of first dose of study drug was specified; -Proportion of patients with a response of clinical cure in the MITT and m-MITT -Populations at Day 5 were added as an additional efficacy endpoint; -Per-pathogen microbiologic eradication rate in the m-MITT and ME-TOC -Populations at the TOC Visit was added as an additional efficacy endpoint; -Treatment failure, per-patient clinical improvement, and recommended minimum duration for clinical evaluation were added to premature discontinuation of study drug; -Staff responsible for documenting and maintaining logs for study drug receipt, storage, preparation, and dispensing were identified; -Procedures for study drugs that experienced a temperature excursion during shipment were provided; -Screening and randomization procedures were clarified, and determination of serum creatinine results within 24 hours of first dose of study drug was added to procedures; -Daily determination of CrCl and daily assessment of vital signs were added to procedures performed during the Treatment Period; -Definition of an adverse event was clarified; -Determination of whether an adverse event was related/not related to study drug was clarified; -PIP-TAZ vial formulation for use in the United States was added; -Changes were also made for clarity and/or consistency. |
|---------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported