

**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
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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
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Arm title	ZTI-01
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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
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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).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	ZTI-01
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Reporting group description: -

Reporting group title	PIP-TAZ
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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.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported