Clinical trial results:
A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP), in Adults

Summary

EudraCT number	2015-001588-37
Trial protocol	EE LV CZ BG PL ES DE HU
Global end of trial date	22 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	ACHN-490-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02486627
WHO universal trial number (UTN)	U1111-1171-1554

Notes:

Sponsors

Sponsor organisation name	Achaogen Inc.
Sponsor organisation address	1 Tower Pl #300,, South San Francisco, United States, 94080
Public contact	Clinical Trials Registration Group, Achaogen, Inc., clinical-trials@achaogen.com
Scientific contact	Clinical Trials Registration Group, Achaogen, Inc., clinical-trials@achaogen.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 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2016
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 the non-inferiority (NI) of plazomicin compared with meropenem based on the difference in composite microbiological eradication and clinical cure rate.

Protection of trial subjects:

This study was conducted in accordance with the US Food and Drug Administration (FDA) regulations, the International Council on Harmonisation (ICH) E6 Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), and applicable local, state, national laws. For European Union member states, this included Directive 2001/20/EC, Directive 2005/28/EC, and other directives as applicable as well as applicable local and national laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Romania: 73
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 80
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Estonia: 51
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Latvia: 57
Country: Number of subjects enrolled	Georgia: 81
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Russian Federation: 79
Country: Number of subjects enrolled	Serbia: 23
Country: Number of subjects enrolled	Ukraine: 72
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	609
EEA total number of subjects	349

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)	326
From 65 to 84 years	271
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 640 subjects were screened and 609 were randomized.

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	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Plazomicin

Arm description:

Subjects received up to 15 milligrams per kilogram (mg/kg) plazomicin as an intravenous (IV) infusion once daily followed by matching placebo infusions 8 and 16 hours later. After a minimum of 4 days of IV plazomicin, subjects could switch to 250 or 500 mg oral levofloxacin for a total duration of 7 to 10 days (IV plus oral).

Arm type	Experimental
Investigational medicinal product name	Plazomicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg as a 30 minute (plus or minus 10 minutes) intravenous (IV) infusion once daily. Dose adjustments, including adjustment of dosing schedule, were required based on renal function.

Investigational medicinal product name	Levofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 or 500 mg once daily depending on renal function to complete a total of 7 to 10 days of IV plus oral therapy

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Saline placebo administered as a 30 minute (plus or minus 10 minutes) intravenous (IV) infusion 8 and 16 hours post plazomicin infusion. Dose adjustments, including adjustment of dosing schedule, were required based on renal function.

Arm title	Meropenem

Arm description:

Subjects received 1.0 g meropenem as an intravenous (IV) infusion every 8 hours (q8h). After a minimum of 4 days of IV meropenem, subjects could switch to 250 or 500 mg oral levofloxacin for a

total duration of 7 to 10 days (IV plus oral).

Arm type	Active comparator
Investigational medicinal product name	Meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 g as a 30 minute (plus or minus 10 minutes) intravenous (IV) infusion every 8 hours (q8h). Dosing schedule adjustments were required based on renal function.

Investigational medicinal product name	Levofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 or 500 mg once daily depending on renal function to complete a total of 7 to 10 days of IV plus oral therapy

Number of subjects in period 1	Plazomicin	Meropenem
Started	306	303
Completed	299	294
Not completed	7	9
Consent withdrawn by subject	4	3
Death	1	-
Other	-	2
Significant patient noncompliance	1	1
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Plazomicin
Reporting group description:	
Subjects received up to 15 milligrams per kilogram (mg/kg) plazomicin as an intravenous (IV) infusion once daily followed by matching placebo infusions 8 and 16 hours later. After a minimum of 4 days of IV plazomicin, subjects could switch to 250 or 500 mg oral levofloxacin for a total duration of 7 to 10 days (IV plus oral).	
Reporting group title	Meropenem
Reporting group description:	
Subjects received 1.0 g meropenem as an intravenous (IV) infusion every 8 hours (q8h). After a minimum of 4 days of IV meropenem, subjects could switch to 250 or 500 mg oral levofloxacin for a total duration of 7 to 10 days (IV plus oral).	

Reporting group values	Plazomicin	Meropenem	Total
Number of subjects	306	303	609
Age categorical Units: Subjects			
Adults (18-64 years)	168	158	326
From 65-84 years	134	137	271
85 years and over	4	8	12
Age continuous Units: years			
arithmetic mean	58.2	59	
standard deviation	± 18.29	± 17.62	-
Gender categorical Units: Subjects			
Female	171	149	320
Male	135	154	289

End points

End points reporting groups

Reporting group title	Plazomicin

Reporting group description:

Subjects received up to 15 milligrams per kilogram (mg/kg) plazomicin as an intravenous (IV) infusion once daily followed by matching placebo infusions 8 and 16 hours later. After a minimum of 4 days of IV plazomicin, subjects could switch to 250 or 500 mg oral levofloxacin for a total duration of 7 to 10 days (IV plus oral).

Reporting group title	Meropenem

Reporting group description:

Subjects received 1.0 g meropenem as an intravenous (IV) infusion every 8 hours (q8h). After a minimum of 4 days of IV meropenem, subjects could switch to 250 or 500 mg oral levofloxacin for a total duration of 7 to 10 days (IV plus oral).

Primary: Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiological Modified Intent to Treat (mMITT) Population at Day 5

End point title	Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiological Modified Intent to Treat (mMITT) Population at Day 5

End point description:

Microbiological eradication was defined as a urine culture that showed the pathogen found at baseline at >=10^5 colony forming units per milliliter (CFU/mL) was reduced to <10^4 CFU/mL. Clinical Cure at Day 5: marked improvement evidenced by complete resolution or return to premorbid levels or reduction in severity of all core baseline symptoms with worsening of none, and no new symptoms developed. Failure: Lack of improvement in core baseline symptoms of complicated urinary tract infection (cUTI) or development of new core symptoms of cUTI; AE requiring the discontinuation of study drug and the patient required alternative non-study antibiotic therapy for the current cUTI. Indeterminate: Insufficient data are available to allow an evaluation of clinical outcome for any reason. The mMTT population subjects received any amount of study drug, had one qualified baseline pathogen where meropenem and plazomicin have antibacterial activity, and no pathogens where they do not have activity.

End point type	Primary

End point timeframe:

Day 5

End point values	Plazomicin	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	197		
Units: Percentage of Subjects				
number (not applicable)				
Composite Cure	88	91.4		
Composite Failure	10.5	7.6		
Indeterminate	1.6	1		

Statistical analyses

Statistical analysis title	Plazomicin vs Meropenem

Statistical analysis description:

95% CIs for the difference in cure rates were calculated using the Newcombe method with continuity correction.

Comparison groups	Plazomicin v Meropenem
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	3.1

Primary: Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiological Modified Intent to Treat (mMITT) Population at Test of Cure (TOC)

End point title	Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiological Modified Intent to Treat (mMITT) Population at Test of Cure (TOC)

End point description:

Microbiological eradication was defined as a urine culture that showed the pathogen found at baseline at >=10^5 colony forming units per milliliter (CFU/mL) was reduced to <10^4 CFU/mL. Clinical Cure at TOC Visit: the complete resolution or return to premorbid levels of core symptoms of cUTI and no new symptoms develop, and no use of non-study antibiotic therapy for the current cUTI. Failure: Persistence of one or more core symptom of infection or reappearance of or development of new core symptoms that require alternative non-study antibiotic therapy for the current cUTI. Indeterminate: Insufficient data are available to allow an evaluation of clinical outcome for any reason. The mMTT population subjects received any amount of study drug, had one qualified baseline pathogen where meropenem and plazomicin have antibacterial activity, and no pathogens where they do not have activity.

End point type	Primary

End point timeframe:

Day 17 TOC Visit

End point values	Plazomicin	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	197		
Units: Percentage of Subjects				
number (not applicable)				
Composite Cure	81.7	70.1		
Composite Failure	15.2	25.9		
Indeterminate	3.1	4.1		

Statistical analyses

Statistical analysis title	Plazomicin vs Meropenem

Statistical analysis description:

95% CIs for the difference in cure rates were calculated using the Newcombe method with continuity correction.

Comparison groups	Meropenem v Plazomicin
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	20.3

Secondary: Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiologically Evaluable (ME) Population at Day 5

End point title	Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiologically Evaluable (ME) Population at Day 5

End point description:

Microbiological eradication: urine culture showed the pathogen found at baseline at >=10^5 colony forming units per milliliter (CFU/mL) was reduced to <10^4 CFU/mL. Clinical Cure Day 5: Marked improvement defined as complete resolution or return to premorbid levels or reduction in severity of all core baseline symptoms with worsening of none, and no new symptoms develop. Failure Day 5: Lack of improvement in core baseline symptoms of cUTI or development of new core symptoms of cUTI; AE requiring the discontinuation of study drug and the subject required alternative non-study antibiotic therapy for the current cUTI. ME population: clinically evaluable subjects with interpretable culture results, defined as one that has clearly identified pathogen(s) or one where baseline pathogen(s) could be excluded.

End point type	Secondary

End point timeframe:

Day 5

End point values	Plazomicin	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	190		
Units: Percentage of Subjects				
number (not applicable)				
Day 5: Composite Cure	89.4	94.2		
Day 5: Composite Failure	10.6	5.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiologically Evaluable (ME) Population at Test of Cure (TOC)

End point title	Percentage of Subjects with a Composite Microbiological Eradication and Clinical Cure in the Microbiologically Evaluable (ME) Population at Test of Cure (TOC)

End point description:

Microbiological eradication: urine culture showed the pathogen found at baseline at >=10^5 colony forming units per milliliter (CFU/mL) was reduced to <10^4 CFU/mL. Clinical Cure TOC: Complete resolution or return to premorbid levels of core symptoms of cUTI and no new symptoms develop, and no use of non-study antibiotic therapy for the current cUTI. Failure TOC: Persistence of one or more core symptom of infection or reappearance of or development of new core symptoms that require alternative non-study antibiotic therapy for the current cUTI.

End point type	Secondary

End point timeframe:

Day 17 TOC Visit

End point values	Plazomicin	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	177		
Units: Percentage of Subjects				
number (not applicable)				
TOC: Composite Cure	84.9	75.1		
TOC: Composite Failure	15.1	24.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered to be drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and it does not imply any judgment about causality. Adverse events also include the exacerbation or worsening of a condition present at screening other than the index infection for which the subject was enrolled in the study. The safety population included all randomised subjects who received any amount of study drug.

End point type	Secondary

End point timeframe:

Up to Day 32

End point values	Plazomicin	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	301		
Units: Percentage of Subjects				
number (not applicable)	19.5	21.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK): Area Under the Curve from 0 to 24 Hours (AUC 0–24h)

End point title	Plasma Pharmacokinetics (PK): Area Under the Curve from 0 to 24 Hours (AUC 0–24h)[1]

End point description:

PK blood samples were collected on Day 3 (plus or minus 1 day) of study drug administration for the determination of plazomicin concentrations in plazomicin-treated patients. The PK Population included subjects who received at least one dose of plazomicin and had at least one quantifiable plazomicin plasma concentration available for analysis.

End point type	Secondary

End point timeframe:

Day 3

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for the meropenem arm are not presented here as PK sample collection does not apply to and was not collected for subjects in the meropenem arm, as only plazomicin levels were measured.

End point values	Plazomicin			
Subject group type	Reporting group			
Number of subjects analysed	281			
Units: mg * h/L				
geometric mean (geometric coefficient of variation)	234 (± 38.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK): Maximum Observed Plasma Drug Concentration (Cmax)

End point title	Plasma Pharmacokinetics (PK): Maximum Observed Plasma Drug Concentration (Cmax)[2]

End point description:

PK blood samples were collected on Day 3 (plus or minus 1 day) of study drug administration for the determination of plazomicin concentrations in plazomicin-treated patients. The PK Population included subjects who received at least one dose of plazomicin and had at least one quantifiable plazomicin plasma concentration available for analysis.

End point type	Secondary

End point timeframe:

Day 3

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for the meropenem arm are not presented here as PK sample collection does not apply to and was not collected for subjects in the meropenem arm, as only plazomicin levels were measured.

End point values	Plazomicin			
Subject group type	Reporting group			
Number of subjects analysed	281			
Units: mg/L				
geometric mean (geometric coefficient of variation)	46.6 (± 43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics (PK): Minimum Observed Plasma Drug Concentration (Cmin)

End point title	Plasma Pharmacokinetics (PK): Minimum Observed Plasma Drug Concentration (Cmin)[3]

End point description:

PK blood samples were collected on Day 3 (plus or minus 1 day) of study drug administration for the determination of plazomicin concentrations in plazomicin-treated patients. The PK Population included subjects who received at least one dose of plazomicin and had at least one quantifiable plazomicin plasma concentration available for analysis.

End point type	Secondary

End point timeframe:

Day 3

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Although it is generally expected that results for primary and secondary endpoints will be presented for all arms included at baseline, results for the meropenem arm are not presented here as PK sample collection does not apply to and was not collected for subjects in the meropenem arm, as only plazomicin levels were measured.

End point values	Plazomicin			
Subject group type	Reporting group			
Number of subjects analysed	281			
Units: mg/L				
geometric mean (geometric coefficient of variation)	0.88 (± 95.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to Day 32

Adverse event reporting additional description:

The AE collection period began with the first dose of study drug and ended at the last follow up visit (LFU). LFU was up to 32 Days after the first dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Plazomicin
Reporting group description: -	
Reporting group title	Meropenem
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious treatment-emergent adverse events in >=5% of patients in any treatment group.

Serious adverse events	Plazomicin	Meropenem	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 303 (1.65%)	5 / 301 (1.66%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic neoplasm			
subjects affected / exposed	1 / 303 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			

subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 303 (0.66%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 303 (0.33%)	0 / 301 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 301 (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 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 303 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 301 (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	Plazomicin	Meropenem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 303 (0.00%)	0 / 301 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2015	The protocol ACHN-490-009 was amended to allow for the inclusion of subjects with moderate renal impairment, defined as a creatinine clearance (CLcr) of >30 to <=60 mL/min as estimated by the Cockcroft-Gault equation. Additional modifications to the protocol were made to better clarify the intent of the existing language in the original protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported