Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of CD101 Injection vs Intravenous Caspofungin Followed By Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia

Summary

EudraCT number	2015-005599-51
Trial protocol	ES GR HU BG BE IT RO
Global end of trial date	13 May 2019

Results information

Result version number	v1 (current)
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	CD101.IV.2.03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02734862
WHO universal trial number (UTN)	-
Other trial identifiers	STRIVE: acronym

Notes:

Sponsors

Sponsor organisation name	Cidara Therapuetics, Inc
Sponsor organisation address	6310 Nancy Ridge Drive, San Diego, United States, 92121
Public contact	Medical Monitoring, Cidara Therapeutics Inc., 001 858249 9459,
Scientific contact	Medical Monitoring, Cidara Therapeutics Inc., 001 858249 9459,

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	16 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2019
Global end of trial reached?	Yes
Global end of trial date	13 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Safety and tolerability of intravenous CD101 (CD101 IV; rezafungin) in the Safety Population
• Overall Success (mycological eradication and resolution of systemic signs attributable to candidemia and/or invasive candidiasis [IC]) of rezafungin in subjects with candidemia and/or IC at Day 14 in the Microbiological Intent-to-treat (mITT) Population

Protection of trial subjects:

The study design was based on the current standard of care for the treatment of canidemia and invasive candidiasis. If a subject had daily blood cultures positive for Candida spp. through Day 7 despite appropriate study drug administration, this was considered an insufficient therapeutic effect and study drug was discontinued and salvage therapy initiated.

Background therapy: -

Evidence for comparator:

Caspofungin and fluconazole were selected as the comparator drug and as the oral step-down drug, respectively, because they are the standard-of-care drugs for first-line and oral treatment, respectively. The dosages of caspofungin and fluconazole were consistent with the Prescribing Information and Infectious Diseases Society of America guidelines.

Actual start date of recruitment	30 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Hungary: 2
Worldwide total number of subjects	207
EEA total number of subjects	128

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)	121
From 65 to 84 years	83
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

There were no patient-facing recruitment materials for this study. Subjects ≥18 years old with ≥1 systemic sign attributable to candidemia and/or invasive candidiasis (IC) and seeking to treat this infection were enrolled .

Pre-assignment

Screening details:

Informed consent, medical history, physical examination, Child-Pugh score (if applicable), modified APACHE II score with Glasgow coma score, vital signs, 12-lead ECG, radiologic test to confirm IC (if applicable), hematology and blood chemistry tests, coagulation panel, urinalysis, pregnancy test, and retinal examination for Candida eye infection

Period 1

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

Blinding implementation details:

The Pharmacy Monitor monitored drug preparation and drug accountability during the study and cases in which unblinding was required due to a safety or tolerability issue. To maintain study blinding, study drug preparation was performed by an unblinded site pharmacist or qualified unblinded personnel at study site not involved with study procedures or evaluation).

Arms

Are arms mutually exclusive?	Yes
Arm title	Rezafungin Group 1

Arm description:

Rezafungin: 400 mg Day 1 and Day 8; optional 400 mg on Day 15, optional for subjects with IC 400 mg Day 22.
Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Arm type	Experimental
Investigational medicinal product name	Rezafungin 400 mg/400 mg
Investigational medicinal product code	CD101
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rezafungin: 400 mg Day 1 and Day 8; optional 400 mg on Day 15, optional for subjects with IC 400 mg Day 22. Placebo control: normal saline to match Caspofungin.

Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	Placebo Infusion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal Saline for infusion on days without Rezafungin administration to maintain blind.

Investigational medicinal product name	microcrystalline cellulose
Investigational medicinal product code	
Other name	oral placebo, encapsulated cellulose
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In order to maintain the blind, subjects in the Rezafungin IV groups who have switched to oral step-down therapy will receive oral placebo (4 capsules on the first day followed by 2 capsules/day thereafter)

Arm title	Rezafungin Group 2

Arm description:

Rezafungin: 400 mg Day 1, 200 mg Day 8; optional 200 mg on Day 15, optional for subjects with IC 200 mg Day 22.Placebo control: normal saline to match Caspofungin.

Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Arm type	Experimental
Investigational medicinal product name	Rezafungin 400 mg/200 mg
Investigational medicinal product code	CD101
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rezafungin: 400 mg Day 1, 200 mg Day 8; optional 200 mg on Day 15, optional for subjects with IC 200 mg Day 22.

Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	Placebo Infusion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal Saline for infusion on days without Rezafungin administration to maintain blind.

Investigational medicinal product name	microcrystalline cellulose
Investigational medicinal product code	
Other name	oral placebo, encapsulated cellulose
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In order to maintain the blind, subjects in the Rezafungin IV groups who have switched to oral step-down therapy will receive oral placebo (4 capsules on the first day followed by 2 capsules/day thereafter)

Arm title	Caspofungin IV

Arm description:

IV Caspofungin (a single 70-mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia).
After ≥3 days of IV therapy, subjects in the Caspofungin group could be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter). After switch to oral step down before Day 8, subjects in the Caspofungin group received IV placebo on Day 8 to preserve the study blind.

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

Dosage and administration details:

70 mg Day 1, 50 mg/day for 14 days, optional 50 mg/day Days 15-21, optional for subjects with IC 50 mg/day Days 22-28.
All subjects received treatment through Day 14 (rezafungin active on Days 1 and 8; caspofungin active Days 1 to 14). Optional additional treatment was available for all subjects on Day 15 (rezafungin groups) or Days 15-21 (caspofungin group). For subjects with IC, additional optional treatment was available on Day 22 (rezafungin groups) or Days 22-28 (caspofungin groups). Subjects with candidemia had a follow-up (FU) Visit on Days 45-52 and subjects with IC had an FU Visit on Days 52-59.

Investigational medicinal product name	Encapsulated Fluconazole
Investigational medicinal product code	
Other name	Fluconazole
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

After ≥3 days of IV therapy, subjects in the caspofungin group can be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter).

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

Dosage and administration details:

After switch to oral step down before Day 8, subjects in the caspofungin group will receive IV placebo on Day 8 to preserve the study blind.

Number of subjects in period 1	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV
Started	81	57	69
Completed	56	42	50
Not completed	25	15	19
Adverse event, serious fatal	11	7	11
Consent withdrawn by subject	4	2	2
Physician decision	2	-	1
Adverse event, non-fatal	2	-	1
Other	1	2	3
noncompliance	1	1	-
Lost to follow-up	4	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Rezafungin Group 1

Reporting group description:

Rezafungin: 400 mg Day 1 and Day 8; optional 400 mg on Day 15, optional for subjects with IC 400 mg Day 22.
Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Reporting group title	Rezafungin Group 2

Reporting group description:

Rezafungin: 400 mg Day 1, 200 mg Day 8; optional 200 mg on Day 15, optional for subjects with IC 200 mg Day 22.Placebo control: normal saline to match Caspofungin.

Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Reporting group title	Caspofungin IV

Reporting group description:

IV Caspofungin (a single 70-mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia).
After ≥3 days of IV therapy, subjects in the Caspofungin group could be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter). After switch to oral step down before Day 8, subjects in the Caspofungin group received IV placebo on Day 8 to preserve the study blind.

Reporting group values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV
Number of subjects	81	57	69
Age categorical			
Eligible subjects were ≥18 years of age, recorded by birth date			
Units: Subjects			
greater than or equal to 65	32	25	29
less than 65	49	32	40
Age continuous			
Units: years			
arithmetic mean	59.4	60.0	59.4
standard deviation	± 15.86	± 15.90	± 15.86
Gender categorical			
eligible subjects were male or females			
Units: Subjects			
Female	37	21	31
Male	44	36	38
Ethnicity			
Number (percent) of participants			
Units: Subjects			
Hispanic or Latino	8	9	7
Not Hispanic or Latino	73	46	59
Unknown or Not Reported	0	2	3

Race			
Number (percent) of participants			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	3
Black or African American	8	7	4
Native Hawaiian or Other Pacific Islander	0	0	0
White	69	44	59
Other	4	2	0
Not reported	0	3	3
APACHE II Category Units: Subjects			
0-9	23	15	17
10-19	39	26	37
Greater than or equal to 20	17	14	9
Missing	2	2	6
Diagnosis Units: Subjects			
Candidemia	62	46	56
Noninvasive candidiasis	19	11	13
Estimated Normalized Creatinine Clearance (mean and standard deviation)			
Estimated Normalized Creatinine clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2			
arithmetic mean	90.8	72.8	87.1
standard deviation	± 52.03	± 52.14	± 59.29
APACHE II Score			
Mean (standard deviation)			
Units: Actual score			
arithmetic mean	13.4	14.1	14.0
standard deviation	± 7.13	± 6.72	± 7.39
Estimated Normalized Creatinine Clearance (median and range)			
Estimated normalized Creatinine Clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2			
median	81.8	57.7	74.4
full range (min-max)	8.1 to 255.4	5.9 to 294.7	7.7 to 278.8
APACHE Score			
APACHE II Score by categories			
Units: Actual score			
median	12.0	14.0	13.0
full range (min-max)	2.0 to 31.0	2.0 to 28.0	1.0 to 35.0

Reporting group values	Total		
Number of subjects	207		
Age categorical			
Eligible subjects were ≥18 years of age, recorded by birth date			
Units: Subjects			

greater than or equal to 65	86		
less than 65	121		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
eligible subjects were male or females			
Units: Subjects			
Female	89		
Male	118		
Ethnicity			
Number (percent) of participants			
Units: Subjects			
Hispanic or Latino	24		
Not Hispanic or Latino	178		
Unknown or Not Reported	5		
Race			
Number (percent) of participants			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Black or African American	19		
Native Hawaiian or Other Pacific Islander	0		
White	172		
Other	6		
Not reported	6		
APACHE II Category			
Units: Subjects			
0-9	55		
10-19	102		
Greater than or equal to 20	40		
Missing	10		
Diagnosis			
Units: Subjects			
Candidemia	164		
Noninvasive candidiasis	43		
Estimated Normalized Creatinine Clearance (mean and standard deviation)			
Estimated Normalized Creatinine clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2			
arithmetic mean			
standard deviation	-		
APACHE II Score			
Mean (standard deviation)			
Units: Actual score			
arithmetic mean			
standard deviation	-		

Estimated Normalized Creatinine Clearance (median and range)			
Estimated normalized Creatinine Clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2 median full range (min-max)	 -		
APACHE Score			
APACHE II Score by categories			
Units: Actual score median full range (min-max)	 -		

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomized to treatment. A subject is considered randomized when a randomization transaction has been recorded in the IWRS, regardless of whether the subject actually received study drug.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomized to treatment and who received any amount of study drug.

Subject analysis set title	Microbiological Intent-to-treat
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of subjects in the Safety population with documented Candida infection based on a Central Laboratory evaluation of an isolate from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site.

Reporting group values	ITT	Safety Population	Microbiological Intent-to-treat
Number of subjects	207	202	183
Age categorical			
Eligible subjects were ≥18 years of age, recorded by birth date			
Units: Subjects			
greater than or equal to 65	86	83	75
less than 65	121	119	108
Age continuous Units: years			
arithmetic mean	59.6	59.4	59.6
standard deviation	± 15.79	± 15.71	± 15.74
Gender categorical			
eligible subjects were male or females			
Units: Subjects			
Female	89	88	79
Male	118	114	104
Ethnicity			
Number (percent) of participants			
Units: Subjects			
Hispanic or Latino	24	24	21

Not Hispanic or Latino	178	173	157
Unknown or Not Reported	5	5	5
Race			
Number (percent) of participants			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	4	4
Black or African American	19	19	16
Native Hawaiian or Other Pacific Islander	0	0	0
White	172	167	153
Other	6	6	6
Not reported	6	6	4
APACHE II Category Units: Subjects			
0-9	55	55	52
10-19	102	101	91
Greater than or equal to 20	40	39	34
Missing	10	7	6
Diagnosis Units: Subjects			
Candidemia	164	159	141
Noninvasive candidiasis	43	43	42
Estimated Normalized Creatinine Clearance (mean and standard deviation)			
Estimated Normalized Creatinine clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2			
arithmetic mean	84.9	84.9	85.3
standard deviation	± 54.78	± 54.78	± 56.14
APACHE II Score			
Mean (standard deviation)			
Units: Actual score			
arithmetic mean	13.8	13.7	13.6
standard deviation	± 7.07	± 7.09	± 7.03
Estimated Normalized Creatinine Clearance (median and range)			
Estimated normalized Creatinine Clearance is based on the Cockroft-Gault formula, normalized to an average height of 1.73 meters, using the lower of actual body weight and ideal body weight to calculate body surface area.			
Units: mL/min/1.73m^2			
median	74.8	74.8	75.3
full range (min-max)	5.9 to 294.7	5.9 to 294.7	5.9 to 294.7
APACHE Score			
APACHE II Score by categories			
Units: Actual score			
median	12.0	12.0	12.0
full range (min-max)	1.0 to 35.0	1.0 to 35.0	1.0 to 35.0

End points

End points reporting groups

Reporting group title	Rezafungin Group 1

Reporting group description:

Rezafungin: 400 mg Day 1 and Day 8; optional 400 mg on Day 15, optional for subjects with IC 400 mg Day 22.
Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Reporting group title	Rezafungin Group 2

Reporting group description:

Rezafungin: 400 mg Day 1, 200 mg Day 8; optional 200 mg on Day 15, optional for subjects with IC 200 mg Day 22.Placebo control: normal saline to match Caspofungin.

Subjects could receive oral step-down therapy after ≥3 days of IV therapy if all criteria were met.
Oral step-down: oral placebo to match fluconazole. Subjects in the rezafungin groups who switched before Day 8 received both oral placebo and rezafungin on Day 8, and if required on Day 15 and Day 22.

Reporting group title	Caspofungin IV

Reporting group description:

IV Caspofungin (a single 70-mg loading dose on Day 1 followed by 50 mg once daily) for ≥3 days up to a maximum of 21 days for subjects with candidemia only and up to a maximum of 28 days for subjects with IC (with or without candidemia).
After ≥3 days of IV therapy, subjects in the Caspofungin group could be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter). After switch to oral step down before Day 8, subjects in the Caspofungin group received IV placebo on Day 8 to preserve the study blind.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomized to treatment. A subject is considered randomized when a randomization transaction has been recorded in the IWRS, regardless of whether the subject actually received study drug.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomized to treatment and who received any amount of study drug.

Subject analysis set title	Microbiological Intent-to-treat
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of subjects in the Safety population with documented Candida infection based on a Central Laboratory evaluation of an isolate from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site.

Primary: Overall Success at Day 14

End point title	Overall Success at Day 14[1]

End point description:

The number and percentage of subjects with an overall success (mycological eradication/presumed eradication and resolution of systemic signs of candidemia and/or IC that were present at baseline)

End point type	Primary

End point timeframe:

Day 14

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: The STRIVE study was not powered for inferential statistics. Therefore, the statistical analysis was uploaded as a separate document.

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Number				
number (not applicable)	46	35	41	

Attachments (see zip file)	Efficacy Endpoint Statistical Analysis/Statistical Analysis for

Statistical analyses

No statistical analyses for this end point

Primary: Overall Incidence of Treatment Emergent Adverse Events (Safety and Tolerability)

End point title	Overall Incidence of Treatment Emergent Adverse Events (Safety and Tolerability)[2]

End point description:

Number of subjects with Incidence of Treatment Emergent Adverse Events based on clinical chemistry, hematology and urine analysis laboratory test, vital signs, physical exams, and ECG abnormalities.

End point type	Primary

End point timeframe:

Treatment-emergent adverse events were recorded from the start of the first infusion of study drug up to Days 42 - 52 for subjects with candidemia only or up to Days 52-59 for subjects with invasive candidiasis, with or without candidiasis.

Notes:

[2] - 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: The STRIVE study was not powered for inferential statistics. Therefore, the statistical analysis was uploaded as a separate document.

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	53	68	
Units: Subjects with one TEAE	71	49	55	

Attachments (see zip file)	Safety Endpoint Statistical Analysis/Statistical Analysis for

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Success at Day 5 and Follow Up

End point title	Overall Success at Day 5 and Follow Up

End point description:

Mycological eradication and resolution of systemic signs attributable to candidemia and/or invasive candidiasis.

End point type	Secondary

End point timeframe:

Day 5

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Number				
number (not applicable)				
Day 5	42	34	34	
Follow-up	36	30	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Mycological Eradication Day 5

End point title	Mycological Eradication Day 5

End point description:

Evaluate mycological success (eradication)

End point type	Secondary

End point timeframe:

Day 5

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Subjects				
number (not applicable)	50	35	38	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Cure at Day 14

End point title	Clinical Cure at Day 14

End point description: Clinical cure was assessed by the Investigator.	
End point type	Secondary
End point timeframe: Day 14 (±1 day)	

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Subjects				
number (not applicable)	53	37	43	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics – evaluate plasma concentrations on Day 1

End point title	Pharmacokinetics – evaluate plasma concentrations on Day 1[3]
End point description: Evaluate plasma concentrations of Rezafungin	
End point type	Secondary
End point timeframe: Day 1, 10 minutes before the end of infusion	

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: Pharmacokinetics were only evaluated on the Rezafungin drug arms (Arms 1 and 2). PK was not evaluated for the comparator arm.

End point values	Rezafungin Group 1	Rezafungin Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: micrograms per milliliter				
arithmetic mean (standard deviation)				
Day 1	15.258 (± 5.5430)	14.743 (± 5.6450)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics – evaluate PK (Cmin)/evaluate minimum plasma concentration (Part A only)/Day 8

End point title	Pharmacokinetics – evaluate PK (Cmin)/evaluate minimum

	plasma concentration (Part A only)/Day 8[4]

End point description:

Evaluate plasma concentrations of Rezafungin

End point type	Secondary

End point timeframe:

Day 8, predose

Notes:

[4] - 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: Pharmacokinetics were only evaluated on the Rezafungin drug arms (Arms 1 and 2). PK was not evaluated for the comparator arm.

End point values	Rezafungin Group 1	Rezafungin Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: micrograms/milliliter				
arithmetic mean (standard deviation)	2.050 (± 0.9767)	2.313 (± 1.2165)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics – evaluate PK (Cmin)/evaluate minimum plasma concentration (Cmin)(Part A only)/Day 15

End point title	Pharmacokinetics – evaluate PK (Cmin)/evaluate minimum plasma concentration (Cmin)(Part A only)/Day 15[5]

End point description:

Evaluate plasma concentrations of Rezafungin

End point type	Secondary

End point timeframe:

Day 15, predose

Notes:

[5] - 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: Pharmacokinetics were only evaluated on the Rezafungin drug arms (Arms 1 and 2). PK was not evaluated for the comparator arm.

End point values	Rezafungin Group 1	Rezafungin Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: micrograms per milliliter				
arithmetic mean (standard deviation)	3.068 (± 1.4565)	2.131 (± 0.8506)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mycological eradication at Day 14

End point title	Mycological eradication at Day 14

End point description:

Evaluate mycological success (eradication)

End point type	Secondary

End point timeframe:

Day 14 (+/- 1 day)

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Subjects				
number (not applicable)	50	35	42	

Statistical analyses

No statistical analyses for this end point

Secondary: Mycological eradication at Follow Up

End point title	Mycological eradication at Follow Up

End point description:

Evaluate mycological success (eradication)

End point type	Secondary

End point timeframe:

Follow-up (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with invasive candidiasis, with or without candidemia).

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Subjects				
number (not applicable)	39	30	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Cure at Follow Up

End point title	Clinical Cure at Follow Up

End point description:

Clinical cure was assessed by the Investigator.

End point type	Secondary

End point timeframe:

follow-up (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with invasive candidiasis, with or without candidemia)

End point values	Rezafungin Group 1	Rezafungin Group 2	Caspofungin IV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	46	61	
Units: Subjects				
number (not applicable)	42	32	38	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected after the signing of the informed consent through to the final visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Rezafungin Group 1

Reporting group description:

Received any study drug exposure in the mITT Population

Reporting group title	Rezafungin Group 2

Reporting group description: -

Reporting group title	Caspofungin group

Reporting group description: -

Serious adverse events	Rezafungin Group 1	Rezafungin Group 2	Caspofungin group
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 81 (43.21%)	28 / 53 (52.83%)	55 / 68 (80.88%)
number of deaths (all causes)	14	6	15
number of deaths resulting from adverse events	14	6	15
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Right ventricular failure			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
generalized edema			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 81 (2.47%)	0 / 53 (0.00%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Gastrointestinal disorders			
abdominal pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 81 (2.47%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ascites			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneocutaneous fistula			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal hemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper gastroin			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
biloma			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
drug induced liver injury			

subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 81 (1.23%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	2 / 53 (3.77%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
candida sepsis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Clostridium difficile colitis			
subjects affected / exposed	2 / 81 (2.47%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diverticulitis			

subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis candida			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Abscess			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	2 / 81 (2.47%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal Abscess			

subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 81 (1.23%)	2 / 53 (3.77%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Septic embolus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	9 / 81 (11.11%)	1 / 53 (1.89%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 8	0 / 1	0 / 2
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	2 / 53 (3.77%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute Respiratory Failure			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	3 / 68 (4.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Apnoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			

subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atelectasis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plural Effusion			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			

subjects affected / exposed	2 / 81 (2.47%)	1 / 53 (1.89%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

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

Non-serious adverse events	Rezafungin Group 1	Rezafungin Group 2	Caspofungin group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 81 (87.65%)	49 / 53 (92.45%)	29 / 68 (42.65%)
Investigations			
Aspiration bronchial			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 81 (2.47%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	2	0	1
Malignant pleural effusion			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Neoplasm malignant			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Post transplant lymphoproliferative disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Femur fracture			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal stoma complication			

subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Post procedural fistula			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Post procedural haematoma			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Tracheal haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 81 (7.41%)	2 / 53 (3.77%)	4 / 68 (5.88%)
occurrences (all)	6	2	4
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Encephalopathy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Metabolic encephalopathy			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Neurodegenerative disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Neurological symptom			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Peroneal nerve palsy			

subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
seizure			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 81 (11.11%)	4 / 53 (7.55%)	6 / 68 (8.82%)
occurrences (all)	9	4	6
Oedema peripheral			
subjects affected / exposed	6 / 81 (7.41%)	2 / 53 (3.77%)	0 / 68 (0.00%)
occurrences (all)	6	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 81 (7.41%)	7 / 53 (13.21%)	4 / 68 (5.88%)
occurrences (all)	6	7	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 81 (8.64%)	11 / 53 (20.75%)	10 / 68 (14.71%)
occurrences (all)	7	11	10
Vomiting			
subjects affected / exposed	6 / 81 (7.41%)	8 / 53 (15.09%)	5 / 68 (7.35%)
occurrences (all)	6	8	5
Nausea			
subjects affected / exposed	4 / 81 (4.94%)	8 / 53 (15.09%)	6 / 68 (8.82%)
occurrences (all)	4	8	6
Abdominal pain			
subjects affected / exposed	5 / 81 (6.17%)	6 / 53 (11.32%)	11 / 68 (16.18%)
occurrences (all)	5	6	11
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	4 / 81 (4.94%)	3 / 53 (5.66%)	3 / 68 (4.41%)
occurrences (all)	4	3	3
Systemic candida			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0

Urosepsis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 81 (4.94%)	4 / 53 (7.55%)	2 / 68 (2.94%)
occurrences (all)	4	4	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 81 (4.94%)	3 / 53 (5.66%)	3 / 68 (4.41%)
occurrences (all)	4	3	3
Haematuria			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	13 / 81 (16.05%)	9 / 53 (16.98%)	9 / 68 (13.24%)
occurrences (all)	13	9	9
Diabetes mellitus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 53 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 53 (1.89%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Metabolic acidosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 53 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2016	1. Revised objectives and other text to expand the definition of overall success to include resolution of systemic signs and symptoms attributable to candidemia, and to evaluate mycological success and clinical cure at additional time points. 2. Added endpoint of overall response. Overall response will be determined programmatically from the mycological response and assessment of clinical signs and symptoms attributable to candidemia, along with definitions of success, failure, and indeterminate. 3. Revised definitions of clinical responses of Cure and Failure for clarity. 4. Clarified timing of blood sample collection for PK analysis. 5. Redefined mITT Population to use a central laboratory evaluation of blood culture. 6. Revised to allow IVD use for mycological diagnosis for enrollment. 7. Revised sample size from 90 to approximately 114 to allow use of IVD (some subjects may be enrolled without positive blood cultures). 8. Clarified exclusion criteria regarding the use of the Child-Pugh score and the timing of the use of other investigational drugs. 9. Added dose adjustments for weight and creatinine clearance. 10. Clarified windows for various evaluations and procedures. 11. Specified that the PI is to assess clinical response. 12. Changed FU Visit from Days 28-35 to Days 45-52. 13. Required additional blood culture closer to randomization. 14. Changed from APACHE II score to modified APACHE II score.
02 September 2016	Italian Specific Amendment. Added justification for use of rezafungin in candidemia treatment.
14 September 2016	1. Removed assessment of subject symptoms and provided further examples of signs of infection. 2. Clarified consideration of subjects with endophthalmitis or indwelling catheters. 3. Added lyophilized formulation of rezafungin, Rezafungin for Injection, and directions for use. Sites will transition from the liquid formulation (CD101 Injection) to the lyophilized formulation (CD101 for Injection). Each subject will receive only one CD101 formulation. Subjects starting on the liquid CD101 will remain on that formulation. 4. Defined stricter criteria for switching to oral therapy and provided safety information on oral fluconazole. 5. Clarified blood collection and processing for PK analysis. 6. Clarified what sites should consider regarding selection of alternative therapy after discontinuation of study treatment.
15 September 2016	German specific amendment. 1. Deleted LAR authority. 2. Clarified consideration of subjects with endophthalmitis or indwelling catheters, and consideration of step-down therapy. 3. Clarified what sites should consider regarding selection of alternative therapy.

23 February 2017	1. Added eligibility of subjects with IC, added treatment, time points, assessments, and descriptions unique to that population. 2. Increased planned study centers to approximately 60 (from approximately 45). 3. Clarified that the Day 15 study drug infusion was optional for all subjects and the Day 22 infusion was an option only for subjects with IC. 4. Added text regarding collecting blood or normally sterile tissue or fluid for culture. 5. Added radiologic tests. 6. Expanded definition of mycological eradication to include normally sterile sites other than blood and definition of presumed mycological eradication. 7. Specified that safety data collection starts when the IC is signed and continues through the FU Visit. 8. Clarified that PK data will be reported separately for the PK Analysis Population.
05 April 2017	Clarified that the FU Visit for all subjects with IC is on Days 52-59.
04 August 2017	1. Added Part B to the study to increase the study sample size; defined procedures, assessments, and analysis. "After approximately 90 subjects have been enrolled in the mITT Population in Part A, enrollment into Part A of the study will close and Part B will begin. In Part B, subjects will be randomized in a 2:1 ratio to receive rezafungin treatment group 1 or IV caspofungin until ≥45 additional subjects and no more than 120 subjects have been enrolled. Total enrollment will depend on the enrollment rate for the 6- to 8-month period between the end of Part A and the start of the Phase 3 study, which is the trigger for Part B to stop enrollment. Oral step-down therapy is allowed in both treatment groups in Part B; oral placebo in the rezafungin group and oral fluconazole in the caspofungin group." 2. Defined that for Part B only, subjects with a positive T2Candida Panel without a positive Candida culture were presumed to have IC. 3. Clarified criteria for oral step-down therapy in Part B for subjects without a positive blood culture but with a positive T2Candida Panel at Screening. 4. Added stopping criteria for IC and T2Candida positive (blood culture negative) subjects. 5. Defined interim analysis procedures for Part A data after Part A database lock. 6. Added that samples will not be collected for PK analysis in Part B. 7. Clarified that only subjects with candidemia require a retinal examination. 8. Changed (from 4 and 8 hours after the start of the infusion to between 15 minutes and 1 hours after the end of the infusion) and added blood collection timepoints (between 2 and 12 hours after the end of the infusion) for samples for PK analysis, clarified PK sample processing procedure.
20 April 2018	1. Changed treatment regimen for subjects randomized to rezafungin treatment in Part B from Group 1 treatment to Group 2 treatment. Clarified that subjects are to complete the protocol version under which they enrolled. 2. Removed use of IVD except for preliminary screening at baseline. 3. Added requirement for 90-day period of contraception use by males. 4. Added Neuropathy and Tremors category of AEs of special interest. 5. Expanded infusion time up to 180 minutes if needed following an infusion reaction. 6. Clarified conditions and procedures for initial and repeated retinal examination. 7. Clarified that due to the staged start of Phase 3, which triggers rolling close of Part B, total enrollment depends on enrollment rate. 8. Replaced description of two formulations with description of a single formulation of lyophilized powder for reconstitution.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported