



Clinical trial results:

An open-label single-arm Phase IIb study of F901318 as treatment of invasive fungal infections due to *Lomentospora prolificans*, *Scedosporium* spp., *Aspergillus* spp., and other resistant fungi in patients lacking suitable alternative treatment options.

Summary

EudraCT number	2017-001290-17
Trial protocol	BE ES NL DE GB PL
Global end of trial date	10 February 2023

Results information

Result version number	v1 (current)
This version publication date	26 June 2024
First version publication date	26 June 2024

Trial information

Trial identification

Sponsor protocol code	F901318/0032
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03583164
WHO universal trial number (UTN)	-
Other trial identifiers	Product INN: : Olorofim

Notes:

Sponsors

Sponsor organisation name	F2G Biotech GmbH
Sponsor organisation address	Seilerstaette 17/13, Innere Stadt, Vienna, Austria, 1010
Public contact	Lesley Fitton, Clinical Operations, F2G Ltd., 44 161785 1270, lfitton@f2g.com
Scientific contact	Lesley Fitton, Clinical Operations, F2G Ltd., 44 161785 1270, lfitton@f2g.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	20 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2023
Global end of trial reached?	Yes
Global end of trial date	10 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Describe the Data Review Committee (DRC)-adjudicated efficacy of F901318 as treatment for infections due to resistant fungi in patients lacking suitable alternative treatment options.

Protection of trial subjects:

Patients given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 2018
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	Netherlands: 16
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	United States: 96
Worldwide total number of subjects	204
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	152
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study planned to enrol approximately 200 patients at approximately 100 centres globally over at least 60 months. The first patient was enrolled into the study on 06 June 2018 and the Last subject last visit date was 10 February 2023 (for the Extended Treatment Phase).

Pre-assignment

Screening details:

Screening assessments were generally completed within the 7 days prior to start of treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Olorofim
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Arm description:

Single arm open label olorofim treatment

Arm type	Experimental
Investigational medicinal product name	Olorofim
Investigational medicinal product code	
Other name	F901318
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Olorofim 30 mg tablets were given for up to 90 days in the Main Study Phase and could be continued for those entering the Extended Treatment Phase.

Patients received a 1-day loading dose of 150 mg of olorofim twice a day followed by a maintenance dose of 90 mg of olorofim twice a day.

Up until Protocol Amendment 06, 58 patients received a weight-based olorofim dosing consisting of a 1-day loading dose of 4 mg/kg/day on Day 1, then a maintenance dose of 2.5 mg/kg/day (divided into 2 or 3 doses). The dose was then adjusted based on plasma levels of olorofim with the maximum total daily dose of 300 mg.

Number of subjects in period 1 ^[1]	Olorofim
Started	203
Completed	126
Not completed	77
Death in Main Phase	35
Lost to follow up in Main Phase	1
Lost to follow up in Extended Phase	3

Clinically significant lab value in Extended Phase	4
Other not specified reason in Main Phase	2
Clinically significant lab value in Main Phase	2
Physician decision in Main Phase	1
Intolerable adverse event in Extended Phase	1
Lack of compliance in Extended Phase	2
Treatment failure in Extended Phase	4
Death in Extended Phase	13
Treatment failure in Main Phase	2
Withdrawal of consent in Extended Phase	2
Intolerable adverse event in Main Phase	3
Physician decision in Extended Phase	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient was enrolled into the trial but did not receive any study treatment. This patient is therefore not included in the Intention to Treat Analysis set which is used as the baseline period of the overall trial.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description:

The overall trial is for the intent to treat (ITT) analysis set which contains all patients in the enrolled set who received at least 1 dose of olorofim. The all patients enrolled set contains all patients who provided written informed consent for this study.

Reporting group values	Overall trial	Total	
Number of subjects	203	203	
Age categorical			
Units: Subjects			
Less than 18 years	0	0	
18 to less than 65 years	151	151	
65 years and over	52	52	
Age continuous			
Units: years			
median	56.57		
full range (min-max)	18.0 to 90.4	-	
Gender categorical			
Units: Subjects			
Female	79	79	
Male	124	124	
Race			
Units: Subjects			
White	160	160	
Black or African American	16	16	
Asian	10	10	
Hawaiian or Pacific Islander	3	3	
Mixed	2	2	
American Indian or Alaska Native	1	1	
Other	3	3	
Not Reported	8	8	
Baseline Data Review Committee- Adjudicated Disease Category			
Units: Subjects			
Aspergillus - All	101	101	
Lomentospora (Scedosporium) prolificans	26	26	
Scedosporium spp.	22	22	
Other Olorofim-susceptible fungi	12	12	
Coccidioides	41	41	
No DRC adjudicated baseline fungus	1	1	
Reason for Limited Treatment Options			
Units: Subjects			
Known/predicted resistance to all licensed agents	42	42	
Failure of available therapy	110	110	
Intolerance to available therapy	29	29	

Inability to manage drug interactions	7	7	
Inability to produce therapeutic drug levels	2	2	
IV only option produced clinical response	10	10	
Other, received Medical Monitor approval	2	2	
Missing	1	1	
Body Mass Index			
Units: kg/m2			
median	22.954		
full range (min-max)	14.21 to 43.23	-	
Duration from Baseline Fungal Infection Start to First Treatment Administration			
Units: Days			
median	75.0		
full range (min-max)	1 to 3821	-	

End points

End points reporting groups

Reporting group title	Olorofim
Reporting group description: Single arm open label olorofim treatment	
Subject analysis set title	Modified Intent to Treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The modified ITT (mITT) set contains all patients in the Intent to Treat analysis set who were assigned to a Data Review Committee adjudicated disease category. The mITT population and sub populations based on the Data Review Committee adjusted disease categories were used for the analysis of efficacy data.	
Subject analysis set title	Intent to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The all patients enrolled set contains all patients who provided written informed consent for this study. The intent to treat (ITT) set contains all patients in the enrolled set who received at least 1 dose of olorofim.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set contains all patients who received at least 1 dose of olorofim, or part thereof.	

Primary: Data Review Committee adjudicated overall response at Day 42

End point title	Data Review Committee adjudicated overall response at Day
End point description: The primary efficacy variable was the Data Review Committee-adjudicated overall response at the Day 42 Study Visit, as determined by an independent Data Review Committee using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. For the primary statistical analysis of overall response rate, values were assigned to the Data Review Committee adjudicated overall response as follows: Success (Success-Complete, Success-Partial); Failure (Failure-Stable, Failure-Progression, Death, and patients for whom data at the Day 42 Study Visit could not be collected or patients who were considered not evaluable at the Day 42 Study Visit).	
End point type	Primary
End point timeframe: 42 days in the Main phase of study treatment	
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: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	28.7 (22.6 to 35.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Data Review Committee adjudicated overall response at Day 42 for All Aspergillus

End point title	Data Review Committee adjudicated overall response at Day 42 for All Aspergillus ^[2]
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End point description:

The primary efficacy variable was the Data Review Committee (DRC)-adjudicated overall response at the Day 42 Study Visit, as determined by an independent DRC using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. This was also presented by each of the 5 major infections as adjudicated by the DRC at baseline. The Aspergillus- All category is a combination of patients with Aspergillus proven and Aspergillus probable (invasive aspergillosis lower respiratory tract disease) baseline disease category. Overall success is defined as a Complete or Partial Response.

End point type	Primary
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End point timeframe:

42 days in the Main phase of study treatment

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: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: Response rate percentage				
number (confidence interval 95%)	34.7 (25.5 to 44.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Data Review Committee adjudicated overall response at Day 42 for Lomentospora prolificans

End point title	Data Review Committee adjudicated overall response at Day 42 for Lomentospora prolificans ^[3]
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End point description:

The primary efficacy variable was the Data Review Committee (DRC)-adjudicated overall response at the Day 42 Study Visit, as determined by an independent DRC using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. This was also presented by each of the 5 major infections

as adjudicated by the DRC at baseline. This one is for patients with proven Invasive Fungal Infection due to Lomentospora prolificans. Success is defined as a Complete or Partial Response.

End point type	Primary
End point timeframe:	
42 days in the Main phase of study treatment	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: Response rate percentage				
number (confidence interval 95%)	42.3 (23.4 to 63.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Data Review Committee adjudicated overall response at Day 42 for Scedosporium species

End point title	Data Review Committee adjudicated overall response at Day 42 for Scedosporium species ^[4]
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End point description:

The primary efficacy variable was the Data Review Committee (DRC)-adjudicated overall response at the Day 42 Study Visit, as determined by an independent DRC using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. This was also presented by each of the 5 major infections as adjudicated by the DRC at baseline. This one is for patients with proven Invasive Fungal Infection due to Scedosporium species. Success is defined as a Complete or Partial Response.

End point type	Primary
End point timeframe:	
42 days in the Main phase of study treatment	

Notes:

[4] - 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: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Response rate percentage				
number (confidence interval 95%)	36.4 (17.2 to 59.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Data Review Committee adjudicated overall response at Day 42 for other olorofim susceptible fungi

End point title	Data Review Committee adjudicated overall response at Day 42 for other olorofim susceptible fungi ^[5]
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End point description:

The primary efficacy variable was the Data Review Committee (DRC)-adjudicated overall response at the Day 42 Study Visit, as determined by an independent DRC using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. This was also presented by each of the 5 major infections as adjudicated by the DRC at baseline. This one is for patients with proven Invasive Fungal Infection due to other olorofim susceptible fungi. Success is defined as a Complete or Partial Response.

End point type	Primary
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End point timeframe:

42 days in the Main phase of study treatment

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Response rate percentage				
number (confidence interval 95%)	33.3 (9.9 to 65.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Data Review Committee adjudicated overall response at Day 42 for Coccidioides species

End point title	Data Review Committee adjudicated overall response at Day 42 for Coccidioides species ^[6]
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End point description:

The primary efficacy variable was the Data Review Committee (DRC)-adjudicated overall response at the Day 42 Study Visit, as determined by an independent DRC using a combination of clinical, mycological, and radiological results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases

Mycoses Study Group (EORTC/MSG) criteria. This was also presented by each of the 5 major infections as adjudicated by the DRC at baseline. This one is for patients with a proven Invasive fungal infection due to *Coccidioides* species. Success is defined as a Complete or Partial Response.

End point type	Primary
End point timeframe:	
42 days in the Main phase of study treatment	

Notes:

[6] - 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: No statistical analysis has been performed as this is a single arm study. 95% confidence intervals are calculated to determine the precision of the estimate.

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Response rate percentage				
number (confidence interval 95%)	0.0 (0.0 to 8.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated overall response at Day 84

End point title	Data Review Committee adjudicated overall response at Day 84
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End point description:

Data Review Committee-adjudicated overall response at Day 84, as determined by an independent Data Review Committee using a combination of clinical, mycological, and radiological results based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. For the analysis of overall response rate, values were assigned to the Data Review Committee adjudicated overall response as follows: Success (Success-Complete, Success-Partial); Failure (Failure-Stable, Failure-Progression, Death, and patients for whom data at the Study Visit could not be collected or patients who were considered not evaluable at the Study Visit).

End point type	Secondary
End point timeframe:	
84 days in the Main phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	27.2 (21.2 to 33.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed overall response at Day 42

End point title	Investigator assessed overall response at Day 42
End point description: Investigator-assessed overall response (as determined by the Investigator using all available assessment results including clinical, mycological and radiologic results based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria) at Day 42, categorised by the same response criteria as in the primary endpoint: Success (Success-Complete, Success-Partial), Failure (Failure-Stable, Failure-Progression, Death, patients for whom data at Day 42 could not be collected or who were considered not evaluable at the specific visit).	
End point type	Secondary
End point timeframe: 42 days in the Main phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	24.8 (19.0 to 31.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed overall response at Day 84

End point title	Investigator assessed overall response at Day 84
End point description: Investigator-assessed overall response (as determined by the Investigator using all available assessment results including clinical, mycological and radiologic results based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria) at Day 84, categorised by the same response criteria as in the primary endpoint: Success (Success-Complete, Success-Partial), Failure (Failure-Stable, Failure-Progression, Death, patients for whom data at Day 84 could not be collected or who were considered not evaluable at the specific visit).	
End point type	Secondary
End point timeframe: 84 days in the Main phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	29.7 (23.5 to 36.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated clinical response at Day 42

End point title	Data Review Committee adjudicated clinical response at Day 42
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End point description:

Data Review Committee adjudicated clinical response at the Day 42 Study Visit, as determined by an independent Data Review Committee using clinical response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Resolution is defined as a Complete or Partial Response.

End point type	Secondary
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End point timeframe:

42 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	59.9 (52.8 to 66.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated clinical response at Day 84

End point title	Data Review Committee adjudicated clinical response at Day 84
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End point description:

Data Review Committee adjudicated clinical response at the Day 84 Study Visit, as determined by an independent Data Review Committee using clinical response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Resolution is defined as a Complete or Partial Response.

End point type	Secondary
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End point timeframe:

84 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	54.0 (46.8 to 61.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed clinical response at Day 42

End point title	Investigator assessed clinical response at Day 42
End point description: Investigator assessed clinical response at the Day 42 Study Visit using clinical response results based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Resolution is defined as a Complete or Partial Response.	
End point type	Secondary
End point timeframe: 42 days in the Main phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	53.5 (46.3 to 60.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed clinical response at Day 84

End point title	Investigator assessed clinical response at Day 84
End point description: Investigator assessed clinical response at the Day 84 Study Visit using clinical response results based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections	

End point type	Secondary
End point timeframe:	
84 days in the Main Phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	56.4 (49.3 to 63.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated mycological response at Day 42

End point title	Data Review Committee adjudicated mycological response at Day 42
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End point description:

Data Review Committee adjudicated mycological response was assessed at the Day 42 Study Visit, as determined by an independent Data Review Committee using mycological response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Success is defined as eradication or presumed eradication.

End point type	Secondary
End point timeframe:	
42 days in the Main Phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	18.3 (13.1 to 24.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated mycological response at Day 84

End point title	Data Review Committee adjudicated mycological response at Day 84
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End point description:

Data Review Committee adjudicated mycological response was assessed at the Day 84 Study Visit, as determined by an independent Data Review Committee using mycological response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Success is defined as eradication or presumed eradication.

End point type	Secondary
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End point timeframe:

84 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	22.5 (16.9 to 28.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed mycological response at Day 42

End point title	Investigator assessed mycological response at Day 42
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End point description:

Mycological response was assessed by the Investigator at the Day 42 Study Visit using mycological response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Success is defined as eradication or presumed eradication.

End point type	Secondary
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End point timeframe:

42 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	25.7 (19.9 to 32.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed mycological response at Day 84

End point title	Investigator assessed mycological response at Day 84
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End point description:

Mycological response was assessed by the Investigator at the Day 84 Study Visit using mycological response results based on European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria. Success is defined as eradication or presumed eradication.

End point type	Secondary
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End point timeframe:

84 days in the Main Phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Response rate percentage				
number (confidence interval 95%)	31.7 (25.3 to 38.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: All cause mortality rate at Day 42

End point title	All cause mortality rate at Day 42
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End point description:

The all cause mortality rate at Day 42 uses the survival status that was entered at the study visit (which employs a window around each nominal study day).

End point type	Secondary
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End point timeframe:

42 days

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Mortality rate percentage				
number (confidence interval 95%)	11.9 (7.8 to 17.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: All cause mortality rate at Day 84

End point title	All cause mortality rate at Day 84
End point description: The all cause mortality rate at Day 84 uses the survival status that was entered at the study visit (which employs a window around each nominal study day).	
End point type	Secondary
End point timeframe: 84 days	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Mortality rate percentage				
number (confidence interval 95%)	16.3 (11.5 to 22.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated radiological response at Day 42

End point title	Data Review Committee adjudicated radiological response at Day 42
End point description: In patients for whom radiology formed a part of their diagnosis, radiology evaluations were required on Day 42 and were adjudicated by an independent Data Review Committee. Radiological responses were assigned as per European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.	
End point type	Secondary
End point timeframe: 42 days in the Main phase of study treatment	

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Number of patients with the response				
≥90% improvement	11			
≥50 to <90% improvement	10			
≥25 to <50% improvement	12			
Stable findings (0% to <25% improvement)	55			
Worsening response	6			
No signs on Radiological images at Screening	7			
Not evaluable	75			
Not relevant	2			
Missing	0			
Death (from any cause)	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Data Review Committee adjudicated radiological response at Day 84

End point title	Data Review Committee adjudicated radiological response at Day 84
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End point description:

In patients for whom radiology formed a part of their diagnosis, radiology evaluations were required on Day 84 and were adjudicated by an independent Data Review Committee. Radiological responses were assigned as per European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.

End point type	Secondary
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End point timeframe:

84 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Number of patients with the response				
≥90% improvement	14			
≥50 to <90% improvement	11			
≥25 to <50% improvement	5			

Stable findings (0% to <25% improvement)	36			
Worsening response	6			
No signs on Radiological images at Screening	5			
Not evaluable	71			
Not relevant	2			
Missing	21			
Death (from any cause)	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed radiological response at Day 42

End point title	Investigator assessed radiological response at Day 42
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End point description:

In patients for whom radiology formed a part of their diagnosis, radiology evaluations were required on Day 42. Radiological responses were assessed by the Investigator using European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.

End point type	Secondary
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End point timeframe:

42 days in the Main phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Number of patients with the response				
≥90% improvement	10			
≥50 to <90% improvement	20			
≥25 to <50% improvement	20			
Stable findings (0% to <25% improvement)	29			
Worsening response	11			
No signs on Radiological images at Screening	3			
Not evaluable	69			
Missing	16			
Death (from any cause)	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator assessed radiological response at Day 84

End point title	Investigator assessed radiological response at Day 84
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End point description:

In patients for whom radiology formed a part of their diagnosis, radiology evaluations were required on Day 84. Radiological responses were assessed by the Investigator using European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.

End point type	Secondary
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End point timeframe:

84 days in the Main Phase of study treatment

End point values	Modified Intent to Treat			
Subject group type	Subject analysis set			
Number of subjects analysed	202			
Units: Number of patients with the response				
≥90% improvement	23			
≥50 to <90% improvement	16			
≥25 to <50% improvement	16			
Stable findings (0% to <25% improvement)	26			
Worsening response	10			
No signs on Radiological images at Screening	4			
Not evaluable	52			
Missing	24			
Death (from any cause)	31			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the time of Informed consent up to and including 4-week post-treatment follow-up.

Adverse event reporting additional description:

Treatment emergent (TE) AEs occurring in main or extended phase are summarised here and defined as any AE which started or worsened on or after the first dose of main phase study treatment up to and including the post-treatment follow-up for the extended phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Olorofim
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Reporting group description:

Single arm open label olorofim treatment.

Serious adverse events	Olorofim		
Total subjects affected by serious adverse events			
subjects affected / exposed	132 / 203 (65.02%)		
number of deaths (all causes)	49		
number of deaths resulting from adverse events	49		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia refractory	Additional description: Acute myeloid leukaemia refractory		
subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Acute myeloid leukaemia	Additional description: Acute myeloid leukaemia		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Blastic plasmacytoid dendritic cell neoplasia	Additional description: Blastic plasmacytoid dendritic cell neoplasia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic myeloid leukaemia	Additional description: Chronic myeloid leukaemia		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diffuse large B-cell lymphoma	Additional description: Diffuse large B-cell lymphoma		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon cancer metastatic	Additional description: Colon cancer metastatic		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm progression	Additional description: Neoplasm progression		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myeloid leukaemia	Additional description: Myeloid leukaemia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression	Additional description: Malignant neoplasm progression		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post transplant lymphoproliferative disorder	Additional description: Post transplant lymphoproliferative disorder		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Skin squamous cell carcinoma recurrent	Additional description: Skin squamous cell carcinoma recurrent		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
T-cell lymphoma	Additional description: T-cell lymphoma		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Aneurysm	Additional description: Aneurysm		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism	Additional description: Embolism		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Apheresis	Additional description: Apheresis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow transplant	Additional description: Bone marrow transplant		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrospinal fluid reservoir	Additional description: Cerebrospinal fluid reservoir placement		

placement			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hospitalisation	Additional description: Hospitalisation		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: Chest pain		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome	Additional description: Multiple organ dysfunction syndrome		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyrexia	Additional description: Pyrexia		
	subjects affected / exposed	9 / 203 (4.43%)	
	occurrences causally related to treatment / all	0 / 11	
	deaths causally related to treatment / all	0 / 0	
Immune system disorders	Additional description: Graft versus host disease		
	Graft versus host disease subjects affected / exposed	1 / 203 (0.49%)	
	occurrences causally related to treatment / all	0 / 1	
	deaths causally related to treatment / all	0 / 0	
Graft versus host disease in lung	Additional description: Graft versus host disease in lung		
	subjects affected / exposed	1 / 203 (0.49%)	
	occurrences causally related to treatment / all	0 / 1	
	deaths causally related to treatment / all	0 / 1	
Respiratory, thoracic and mediastinal disorders	Additional description: Acute respiratory failure		
	Acute respiratory failure subjects affected / exposed	4 / 203 (1.97%)	
	occurrences causally related to treatment / all	0 / 4	
	deaths causally related to treatment / all	0 / 2	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
	subjects affected / exposed	1 / 203 (0.49%)	
	occurrences causally related to treatment / all	0 / 1	
	deaths causally related to treatment / all	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
	subjects affected / exposed	5 / 203 (2.46%)	
	occurrences causally related to treatment / all	0 / 8	
	deaths causally related to treatment / all	0 / 1	
Haemoptysis	Additional description: Haemoptysis		
	subjects affected / exposed	2 / 203 (0.99%)	
	occurrences causally related to treatment / all	0 / 4	
	deaths causally related to treatment / all	0 / 0	
Haemothorax	Additional description: Haemothorax		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Mediastinal mass	Additional description: Mediastinal mass		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage	Additional description: Pulmonary haemorrhage		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Pneumothorax spontaneous	Additional description: Pneumothorax spontaneous		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain	Additional description: Pleuritic pain		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion	Additional description: Pleural effusion		

subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder	Additional description: Respiratory disorder		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	8 / 203 (3.94%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 5		
Psychiatric disorders			
Suicidal ideation	Additional description: Suicidal ideation		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device breakage	Additional description: Device breakage		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device malfunction	Additional description: Device malfunction		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device leakage	Additional description: Device leakage		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatic enzyme increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hepatic enzyme increased		
	7 / 203 (3.45%)		
	4 / 10		
	0 / 0		
Liver function test increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Liver function test increased		
	7 / 203 (3.45%)		
	1 / 7		
	0 / 0		
Transaminases increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Transaminases increased		
	1 / 203 (0.49%)		
	1 / 1		
	0 / 0		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Fall		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Femoral neck fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Femoral neck fracture		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Complications of transplanted lung subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Complications of transplanted lung		
	2 / 203 (0.99%)		
	0 / 2		
	0 / 0		
Head injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Head injury		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Hip fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hip fracture		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		

Pseudomeningocele subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pseudomeningocele		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Postoperative wound complication subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Postoperative wound complication		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Shunt malfunction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Shunt malfunction		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Skin laceration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Skin laceration		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Spinal fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Spinal fracture		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Wound subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Wound		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Wound dehiscence subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Wound dehiscence		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Cardiac disorders Acute myocardial infarction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Acute myocardial infarction		
	1 / 203 (0.49%)		
	0 / 1		
	0 / 0		
Atrial fibrillation	Additional description: Atrial fibrillation		

subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute	Additional description: Cardiac failure acute		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure	Additional description: Left ventricular failure		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulseless electrical activity	Additional description: Pulseless electrical activity		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion	Additional description: Pericardial effusion		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia	Additional description: Sinus bradycardia		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic cardiomyopathy	Additional description: Toxic cardiomyopathy		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Arachnoid cyst	Additional description: Arachnoid cyst		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage	Additional description: Cerebral haemorrhage		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident	Additional description: Cerebrovascular accident		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache	Additional description: Headache		
subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus	Additional description: Hydrocephalus		

subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intraventricular haemorrhage	Additional description: Intraventricular haemorrhage		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder	Additional description: Nervous system disorder		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolic encephalopathy	Additional description: Metabolic encephalopathy		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningism	Additional description: Meningism		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy	Additional description: Lethargy		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope	Additional description: Presyncope		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior reversible encephalopathy syndrome	Additional description: Posterior reversible encephalopathy syndrome		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure	Additional description: Seizure		

subjects affected / exposed	4 / 203 (1.97%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Somnolence	Additional description: Somnolence		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression	Additional description: Spinal cord compression		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus	Additional description: Status epilepticus		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage	Additional description: Subarachnoid haemorrhage		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thalamic stroke	Additional description: Thalamic stroke		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation	Additional description: Disseminated intravascular coagulation		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neutropenia	Additional description: Neutropenia		

subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Exophthalmos	Additional description: Exophthalmos		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye pain	Additional description: Eye pain		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papilloedema	Additional description: Papilloedema		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment	Additional description: Retinal detachment		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcerative keratitis	Additional description: Ulcerative keratitis		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis	Additional description: Gastritis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage	Additional description: Gastrointestinal haemorrhage		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ileus	Additional description: Ileus		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction	Additional description: Intestinal obstruction		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea	Additional description: Nausea		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury	Additional description: Drug-induced liver injury		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis	Additional description: Acute febrile neutrophilic dermatosis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Anuria	Additional description: Anuria		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment	Additional description: Renal impairment		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		

subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovial cyst	Additional description: Synovial cyst		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis	Additional description: Rhabdomyolysis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebral column mass	Additional description: Vertebral column mass		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal sepsis	Additional description: Abdominal sepsis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Abscess limb	Additional description: Abscess limb		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis fungal	Additional description: Arthritis fungal		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis infective	Additional description: Arthritis infective		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspergillus infection	Additional description: Aspergillus infection		
subjects affected / exposed	4 / 203 (1.97%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Bacteraemia	Additional description: Bacteraemia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection	Additional description: Bacterial infection		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain abscess	Additional description: Brain abscess		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis	Additional description: Bronchopulmonary aspergillosis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Candida infection	Additional description: Candida infection		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection	Additional description: Catheter site infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial	Additional description: Arthritis bacterial		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis	Additional description: Device related sepsis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Disseminated aspergillosis	Additional description: Disseminated aspergillosis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Disseminated coccidioidomycosis	Additional description: Disseminated coccidioidomycosis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Enterococcal infection	Additional description: Enterococcal infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CNS ventriculitis	Additional description: CNS ventriculitis		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coccidioidomycosis	Additional description: Coccidioidomycosis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
COVID-19	Additional description: COVID-19		
subjects affected / exposed	8 / 203 (3.94%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus viraemia	Additional description: Cytomegalovirus viraemia		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Fungal endocarditis	Additional description: Fungal endocarditis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Fungal skin infection	Additional description: Fungal skin infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis bacterial	Additional description: Gastroenteritis bacterial		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral	Additional description: Gastroenteritis viral		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis	Additional description: Intervertebral discitis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis externa	Additional description: Otitis externa		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis	Additional description: Osteomyelitis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mycobacterium chelonae infection	Additional description: Mycobacterium chelonae infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mycetoma mycotic	Additional description: Mycetoma mycotic		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metapneumovirus infection	Additional description: Metapneumovirus infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis coccidioides	Additional description: Meningitis coccidioides		

subjects affected / exposed	5 / 203 (2.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Meningitis	Additional description: Meningitis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis	Additional description: Klebsiella sepsis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal abscess	Additional description: Renal abscess		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Purulent discharge	Additional description: Purulent discharge		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis	Additional description: Pulmonary sepsis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Psoas abscess	Additional description: Psoas abscess		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomembranous colitis	Additional description: Pseudomembranous colitis		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection	Additional description: Postoperative wound infection		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral	Additional description: Pneumonia viral		
subjects affected / exposed	3 / 203 (1.48%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia klebsiella	Additional description: Pneumonia klebsiella		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia haemophilus	Additional description: Pneumonia haemophilus		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia fungal	Additional description: Pneumonia fungal		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	13 / 203 (6.40%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 3		
Picornavirus infection	Additional description: Picornavirus infection		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: Sepsis		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Septic arthritis staphylococcal	Additional description: Septic arthritis staphylococcal		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock	Additional description: Septic shock		
subjects affected / exposed	4 / 203 (1.97%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection bacterial	Additional description: Respiratory tract infection bacterial		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhodococcus infection	Additional description: Rhodococcus infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urosepsis	Additional description: Urosepsis		

subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound sepsis	Additional description: Wound sepsis		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection	Additional description: Wound infection		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection staphylococcal	Additional description: Wound infection staphylococcal		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia	Additional description: Hypoglycaemia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	2 / 203 (0.99%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia	Additional description: Hypophosphataemia		

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Olorofim		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 203 (91.63%)		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	11 / 203 (5.42%)		
occurrences (all)	12		
Hypotension	Additional description: Hypotension		
subjects affected / exposed	16 / 203 (7.88%)		
occurrences (all)	21		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	18 / 203 (8.87%)		
occurrences (all)	19		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	19 / 203 (9.36%)		
occurrences (all)	21		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	29 / 203 (14.29%)		
occurrences (all)	41		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	15 / 203 (7.39%)		
occurrences (all)	17		
Cough	Additional description: Cough		
subjects affected / exposed	19 / 203 (9.36%)		
occurrences (all)	19		
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	Additional description: Depression		
	13 / 203 (6.40%)		
	13		
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all) Liver function test increased subjects affected / exposed occurrences (all)	Additional description: Hepatic enzyme increased		
	18 / 203 (8.87%)		
	22		
	Additional description: Liver function test increased		
	22 / 203 (10.84%)		
	27		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	Additional description: Headache		
	32 / 203 (15.76%)		
	42		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	Additional description: Anaemia		
	12 / 203 (5.91%)		
	16		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	Additional description: Abdominal pain		
	13 / 203 (6.40%)		
	17		
	Additional description: Diarrhoea		
	42 / 203 (20.69%)		
	51		
	Additional description: Constipation		
	15 / 203 (7.39%)		
	17		
	Additional description: Vomiting		
	40 / 203 (19.70%)		
	54		
	Additional description: Nausea		
	40 / 203 (19.70%)		
	53		
Skin and subcutaneous tissue disorders Rash			
	Additional description: Rash		

subjects affected / exposed occurrences (all)	11 / 203 (5.42%) 13		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed occurrences (all)	15 / 203 (7.39%) 15		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed occurrences (all)	15 / 203 (7.39%) 23		
Back pain	Additional description: Back pain		
subjects affected / exposed occurrences (all)	14 / 203 (6.90%) 14		
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed occurrences (all)	13 / 203 (6.40%) 14		
Infections and infestations			
COVID-19	Additional description: COVID-19		
subjects affected / exposed occurrences (all)	18 / 203 (8.87%) 19		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed occurrences (all)	17 / 203 (8.37%) 24		
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed occurrences (all)	16 / 203 (7.88%) 22		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed occurrences (all)	11 / 203 (5.42%) 11		
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed occurrences (all)	14 / 203 (6.90%) 14		
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed occurrences (all)	12 / 203 (5.91%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2018	Amendment 01. The frequency of orlofim dosing was changed based on emerging data from Phase I studies in healthy volunteers. The frequency of blood sample collection when intensive pharmacokinetics is being assessed was amended to be consistent with the change in dose frequency.
02 May 2018	Amendment 02. The loading and maintenance orlofim doses were changed from fixed doses to weight-related doses. The frequency of dosing with orlofim, and the rationale for the dose adjustment were changed based on emerging data from Phase I studies in healthy volunteers. A maximum daily dose, which was not previously defined, was added to the Protocol. The exclusion of patients with HIV infection was modified to allow the inclusion of patients with newly diagnosed HIV infection.
28 November 2018	Amendment 03. The descriptions of End Of Treatment and End Of Study were updated to clarify the process for patients who received Extended Treatment with orlofim beyond the 90 days. The inclusion criteria were updated to describe the process for enrolment of patients with multiple fungal infections. Concomitant administration of inhibitors of human dihydro-orotate dehydrogenase were considered prohibited. Additional information was included on the rationale for the sample size and the comparisons to be conducted on the study data. The definition of adverse events of special interest was updated.
03 May 2019	Amendment 04. An Extended Treatment phase was added to the study to allow continued treatment with orlofim for patients who have benefited from treatment with orlofim during the 90 day study treatment period, have no suitable alternative treatment options and would continue to benefit from extended treatment. Patient-reported outcomes were added which included the inclusion of a dedicated secondary objective. Discontinuation criteria were updated and guidance on dose interruptions was also included.
28 February 2020	Amendment 06. The number of patients and number of centres were increased. Sample size calculations in support of the increased number of patients were included. Patient-reported outcomes were added as an objective during the Extended Treatment Phase. An initial analysis of data was included. Inclusion criterion 1 was updated to include patients aged 16 years or 17 years and who weighing at least 40 kg. The orlofim dose was defined as 150 mg twice daily (loading dose) and 90 mg twice daily (maintenance dose). References to therapeutic drug monitoring and subsequent dose adjustment of orlofim based upon trough levels were removed. Updates were made to the reporting requirements for adverse events of special interest.

07 April 2020	Coronavirus Disease 2019 (COVID 19) Interim Protocol Addendum. In light of the impact of COVID-19 pandemic on clinical trial conduct, and in accordance with regulatory guidance issued by FDA and EMA, the Sponsor concluded that the life-threatening nature of the infections in Study 32 participants warrants continued therapy of existing patients and continued enrolment of new patients. This addendum intended to immediately implement selected study procedure simplifications (that were also being submitted to study sites as part of Amendment 6 (28 February 2020)).
01 May 2020	Coronavirus Disease 2019 (COVID 19) Interim Protocol Addendum number 2. Further risk assessment of Study 32 performed at the recommendation of regulatory guidance (eg., FDA, and EMA) concluded an alternative route of administration is beneficial for patients who are unable to swallow tablets. This addendum allowed the use of tablet in water formulation for dosing by a nasogastric tube under exceptional circumstances.
12 June 2020	Electrocardiogram Sub-study Protocol Addendum. To fulfil regulatory requirements, time-matched PK samples and ECG recordings were to be collected in a subset of patients at selected sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported