



Clinical trial results:

A multicentre, double blind, randomised, placebo controlled, Phase II trial to evaluate Resminostat for maintenance treatment of patients with advanced stage (Stage IIB-IVB) mycosis fungoides (MF) or Sézary Syndrome (SS) that have achieved disease control with systemic therapy – the RESMAIN Study

Summary

EudraCT number	2016-000807-99
Trial protocol	GB DE NL ES AT BE PL GR IT
Global end of trial date	08 August 2024

Results information

Result version number	v1 (current)
This version publication date	17 July 2025
First version publication date	17 July 2025
Summary attachment (see zip file)	CTR Synopsis (CTR 4SC-201-6-2015_final analyses_V 3.0_22Nov2024_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	4SC-201-6-2015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02953301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	4SC AG
Sponsor organisation address	Fraunhoferstr. 22, Planegg, Germany, 82152
Public contact	Corporate Communications, 4SC AG, public@4sc.com
Scientific contact	Clinical Operations, 4SC AG, resmain@4sc.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	08 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2023
Global end of trial reached?	Yes
Global end of trial date	08 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if maintenance treatment with resminostat increases progression-free survival (PFS) compared to placebo in patients with advanced stage (Stage IIB-IVB) MF or SS that have achieved disease control (complete response [CR], partial response [PR] or stable disease [SD]) with previous systemic therapy.

Protection of trial subjects:

The most recent systemic therapy had to have been completed as planned or stopped due to unacceptable tolerability prior to randomisation to prevent discontinuation of patients from treatments from which they derived benefit. All patients, including those randomised to treatment with placebo, were able to receive best supportive care at the discretion of the investigator. Patients randomised to treatment with placebo who had disease progression were offered to roll over to resminostat. Before the start of a new treatment cycle, subjects were assessed including adverse events, physical examination, and measurement of hematological and biochemical parameters. Depending on the observed toxicities, the dose of resminostat could be individually reduced by 1/3 of the total daily dose. Guidance was given in the study protocol concerning actions to be taken due to the observed toxicities (dose reduction, interruption, discontinuation). Subjects requiring more than one dose reduction had to be discontinued.

A Data Safety Monitoring Board (DSMB) was implemented to independently safeguard the interests of patients in the study and to enhance the integrity and credibility of the study. The DSMB reviewed selected safety data across the study at regular, pre-defined intervals and made recommendations regarding continuation, modification or termination of the study for safety concerns.

Background therapy: -

Evidence for comparator:

The use of placebo as a treatment arm was considered justified since medical guidelines did not give clear recommendations for maintenance treatment in advanced CTCL, as evidence-based information on maintenance treatment is missing. Furthermore, patients on placebo had the option to roll-over to open-label treatment with resminostat once progressive. The Sponsor's opinion on use of placebo was confirmed by the EMA (Scientific Advice: EMA/CHMP/SAWP/ 33911/2016, 28-Jan-2016).

Actual start date of recruitment	14 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 23
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Italy: 18
Worldwide total number of subjects	201
EEA total number of subjects	141

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)	104
From 65 to 84 years	96
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Eligible patients were randomized to treatment with resminostat or placebo at a ratio of 1:1 using IWRS, from 09 Jan 2017 to 11 May 2022 at 55 sites in 12 countries.

Randomization of patients to resminostat or placebo was stratified by disease stage prior to the last systemic therapy and remission status achieved with the last systemic therapy.

Pre-assignment

Screening details:

234 patients (including 11 patients who were re-screened and thus each counted twice) were screened for trial participation. Of these, 33 were screening failures due to eligibility criterion not met (n=18), patient withdrawal (n=4), adverse event (n=4), physician decision (n=1) or other reasons (n=6), but 11 were eligible upon re-screening.

Period 1

Period 1 title	Randomized period (double-blind)
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:

Randomization (including stratification) of an individual patient to resminostat or placebo treatment was performed according to an algorithm in the IWRS. Subsequently to stratification and randomization, the IWRS assigned a specific medication kit (per kit number) to each patient. The kit numbers were assigned to wallets, each containing one resminostat or placebo blister. Emergency unblinding for a patient was also performed via the IWRS by the investigator or authorized team members.

Arms

Are arms mutually exclusive?	Yes
Arm title	Resminostat - ITT

Arm description:

Subjects who were randomized to treatment with resminostat and included in the Intention to Treat population.

Arm type	Experimental
Investigational medicinal product name	Resminostat
Investigational medicinal product code	4SC-201
Other name	KINSELBY
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each treatment consisted of 3 tablets (600 mg), administered orally once daily, from Day 1 – Day 5 of each 14 day cycle. Tablets were to be taken together, preferably in the morning, with water, and could be administered with or without food. The tablets were not to be chewed and/or crushed but were to be swallowed whole.

Arm title	Placebo - ITT
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Arm description:

Subjects who were randomized to treatment with placebo and included in the Intention to Treat population.

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

Dosage and administration details:

Each treatment consisted of 3 tablets, administered orally once daily, from Day 1 – Day 5 of each 14 day cycle. Tablets were to be taken together, preferably in the morning, with water, and could be administered with or without food. The tablets were not to be chewed and/or crushed but were to be swallowed whole.

Number of subjects in period 1	Resminostat - ITT	Placebo - ITT
Started	100	101
Completed	100	101

Period 2

Period 2 title	Rollover Period (open-label)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients randomized to treatment with placebo who progressed were offered to roll over to resminostat.

Arms

Arm title	Open-label
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Arm description:

Subjects treated with placebo in the randomized period, who progressed and agreed to roll over to open-label treatment with resminostat.

Arm type	Experimental
Investigational medicinal product name	Resminostat
Investigational medicinal product code	4SC-201
Other name	KINSELBY
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each treatment consisted of 3 tablets (600 mg), administered orally once daily, from Day 1 – Day 5 of each 14 day cycle. Tablets were to be taken together, preferably in the morning, with water, and could be administered with or without food. The tablets were not to be chewed and/or crushed but were to be swallowed whole.

Number of subjects in period 2 ^[1]	Open-label
Started	80
Completed	80

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all patients had the option to enter the Rollover Period. Only patients on placebo who progressed during the double-blind phase, or patients on blinded treatment at trial termination had the option to roll-over to open-label treatment with resminostat (Rollover Period).

Baseline characteristics

Reporting groups

Reporting group title	Resminostat - ITT
Reporting group description: Subjects who were randomized to treatment with resminostat and included in the Intention to Treat population.	
Reporting group title	Placebo - ITT
Reporting group description: Subjects who were randomized to treatment with placebo and included in the Intention to Treat population.	

Reporting group values	Resminostat - ITT	Placebo - ITT	Total
Number of subjects	100	101	201
Age categorical			
Units: Subjects			
Adults (18-64 years)	53	51	104
From 65-84 years	46	50	96
85 years and over	1	0	1
Age continuous			
Units: years			
median	63.5	64.0	
standard deviation	± 11.8	± 12.1	-
Gender categorical			
Units: Subjects			
Female	47	31	78
Male	53	70	123
Diagnosis			
Units: Subjects			
Mycosis fungoides	80	84	164
Sézary Syndrome	20	17	37
Remission status			
Randomization of subjects to resminostat or placebo was stratified by disease stage prior to the last systemic therapy and remission status achieved with the last systemic therapy to ensure comparability of the populations in the two treatment arms.			
Units: Subjects			
Complete Response	14	11	25
Partial Response	49	58	107
Stable Disease	37	32	69
Stage of disease			
Subjects with advance stage (Stages IIB to IVB) Mycosis fungoides or Sézary syndrome were enrolled in this study.			
Units: Subjects			
IIB	59	58	117
IIIA	8	4	12
IIIB	7	4	11
IVA1	10	16	26
IVA2	13	13	26
IVB	3	6	9

Subject analysis sets

Subject analysis set title	Resminostat - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Includes all patients who were correctly randomised to resminostat and treated accordingly with at least one dose of the trial medication and who did not have any major protocol violations. Patients were analysed as treated.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Includes all patients who were correctly randomised to placebo and treated accordingly with at least one dose of the trial medication and who did not have any major protocol violations. Patients were analysed as treated.

Reporting group values	Resminostat - PP	Placebo - PP	
Number of subjects	90	84	
Age categorical			
Units: Subjects			
Adults (18-64 years)	47	39	
From 65-84 years	42	45	
85 years and over	1	0	
Age continuous			
Units: years			
median	63.5	65.0	
standard deviation	± 11.7	± 12.1	
Gender categorical			
Units: Subjects			
Female	40	29	
Male	50	55	
Diagnosis			
Units: Subjects			
Mycosis fungoides	71	68	
Sézary Syndrome	19	16	
Remission status			
Randomization of subjects to resminostat or placebo was stratified by disease stage prior to the last systemic therapy and remission status achieved with the last systemic therapy to ensure comparability of the populations in the two treatment arms.			
Units: Subjects			
Complete Response	11	10	
Partial Response	46	49	
Stable Disease	33	25	
Stage of disease			
Subjects with advance stage (Stages IIB to IVB) Mycosis fungoides or Sézary syndrome were enrolled in this study.			
Units: Subjects			
IIB	53	44	
IIIA	7	4	
IIIB	7	4	
IVA1	9	15	
IVA2	11	13	
IVB	3	4	

End points

End points reporting groups

Reporting group title	Resminostat - ITT
Reporting group description: Subjects who were randomized to treatment with resminostat and included in the Intention to Treat population.	
Reporting group title	Placebo - ITT
Reporting group description: Subjects who were randomized to treatment with placebo and included in the Intention to Treat population.	
Reporting group title	Open-label
Reporting group description: Subjects treated with placebo in the randomized period, who progressed and agreed to roll over to open-label treatment with resminostat.	
Subject analysis set title	Resminostat - PP
Subject analysis set type	Per protocol
Subject analysis set description: Includes all patients who were correctly randomised to resminostat and treated accordingly with at least one dose of the trial medication and who did not have any major protocol violations. Patients were analysed as treated.	
Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol
Subject analysis set description: Includes all patients who were correctly randomised to placebo and treated accordingly with at least one dose of the trial medication and who did not have any major protocol violations. Patients were analysed as treated.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description: PFS was defined as the time from date of randomisation to first date that criteria for progressive disease were met according to the global response score or death due to any cause in the absence of documented progressive disease.	
End point type	Primary
End point timeframe: From date of randomisation to end of blinded treatment.	

End point values	Resminostat - ITT	Placebo - ITT	Resminostat - PP	Placebo - PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	100	101	90	84
Units: months				
median (confidence interval 95%)	8.3 (4.2 to 15.7)	4.2 (2.8 to 6.4)	8.2 (4.2 to 15.2)	3.7 (2.8 to 4.7)

Statistical analyses

Statistical analysis title	Analysis of the Primary Endpoint
Statistical analysis description: A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata. Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.424
upper limit	0.916

Secondary: Time to Symptom (Pruritus) Worsening (TTSW)

End point title	Time to Symptom (Pruritus) Worsening (TTSW)
End point description: TTSW (pruritus), the key secondary endpoint, is defined as the time from date of randomisation to first date that criteria for symptom (pruritus) worsening were met. Symptom worsening was defined as an increase of a minimum of 3 points on the visual analogue scale (VAS) itching score, confirmed by two consecutive VAS itching score assessments (total of four weeks/two cycles) by the subject.	
End point type	Secondary
End point timeframe: From date of randomisation to end of blinded treatment.	

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	82		
Units: Subjects with event	14	11		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint TTSW
Statistical analysis description: A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata. Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.644
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.215
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.538
upper limit	2.742

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	
TTP was defined as the time from date of randomisation to first date that criteria for progressive disease (per the global response score) were met.	
End point type	Secondary
End point timeframe:	
From date of randomisation to end of blinded treatment.	

End point values	Resminostat - ITT	Placebo - ITT	Resminostat - PP	Placebo - PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	100	101	90	84
Units: months				
median (confidence interval 95%)	8.3 (4.2 to 15.7)	4.2 (2.8 to 6.4)	8.2 (4.2 to 15.2)	3.7 (2.8 to 4.7)

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint TTP
Statistical analysis description:	
A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.623

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.424
upper limit	0.916

Secondary: Time to Next Treatment (TTNT)

End point title	Time to Next Treatment (TTNT)
End point description:	
TTNT was defined as the time from date of randomisation to first date that new treatment was received. For placebo patients, rollover to resminostat was considered as the next treatment.	
End point type	Secondary
End point timeframe:	
From date of randomisation to end of follow-up.	

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: months				
median (confidence interval 95%)	8.8 (7.4 to 13.8)	4.2 (3.0 to 6.0)		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint TTNT
Statistical analysis description:	
A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.594
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.428
upper limit	0.825

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
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End point description:

ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response during the randomised period. Therefore, patients with baseline remission status of complete response were excluded from this analysis. The response reported by the Investigator was used for the analysis. Only Global Response Scores that were based on all four components were considered for the evaluation of the ORR.

End point type	Secondary
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End point timeframe:

From date of randomisation to end of blinded treatment.

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: subjects				
Complete Response	3	0		
Partial Response	12	9		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint ORR
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Statistical analysis description:

Odds Ratio and its related p-value from a Cochran-Mantel-Haenszel (CMH) test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.

Comparison groups	Resminostat - ITT v Placebo - ITT
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Number of subjects included in analysis	176
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.12
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Method	Cochran-Mantel-Haenszel
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Parameter estimate	Odds ratio (OR)
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Point estimate	2.022
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.764
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upper limit	5.565
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Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

DOR was defined as the time from date of complete response or partial response (whichever is first) until the criteria for progressive disease (per global response score) were met.
For patients who achieved a partial response (PR) or complete response (CR) during the trial, DOR was calculated as the number of months from the date measurement criteria were first met for a PR or CR (whichever was recorded first) as determined by global response score assessment (based on four components) until the first date that PD was determined by global response score assessment. Patients with baseline remission status CR were excluded from this analysis. DOR was calculated as (date of first PD - date of PR/CR) + 1.

End point type	Secondary
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End point timeframe:

From date of randomisation to end of blinded treatment.

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	12		
Units: months				
number (not applicable)	19.4	20.3		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint DOR
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Statistical analysis description:

A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.

Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.

Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.287
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.579
upper limit	9.024

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall Survival is defined as the time from the day of randomisation to death from any cause.
For patients who are known to be still alive at the time of trial analysis or who are lost to FU, survival

time will be censored at the last recorded date that the patient is known to be alive (i.e. the date of last attended visit or the date of the follow-up phone call). Not only data from randomised period but also rollover and follow-up data will be taken into account for derivation of overall survival.

End point type	Secondary
End point timeframe:	
Time from the day of randomisation to end of follow-up.	

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: months				
number (not applicable)	70.8	75.6		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint OS
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Statistical analysis description:

A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.

Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.

Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.606
upper limit	1.59

Secondary: Progression Free Survival on Second Line Therapy (PFS2)

End point title	Progression Free Survival on Second Line Therapy (PFS2)
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End point description:

PFS2 was defined as the time from date of randomisation to second objective disease progression or death from any cause (whichever comes first).

If a patient started first subsequent treatment before first objective disease progression, then the first objective disease progression prior to start of the second subsequent treatment was considered as event.

For the placebo treatment group, PFS2 was assessed in rollover period or (if no rollover took place) in follow-up period. For the resminostat treatment group, PFS2 was assessed in follow-up period.

End point type	Secondary
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End point timeframe:

From date of randomisation to end of follow-up.

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: months				
median (confidence interval 95%)	26.5 (20.0 to 48.3)	23.2 (16.6 to 33.6)		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint PFS2
Statistical analysis description: A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata. Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.758
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.516
upper limit	1.113

Secondary: Progression Free Survival on Third Line Therapy (PFS3)

End point title	Progression Free Survival on Third Line Therapy (PFS3)
End point description: PFS3 was defined as the time from date of randomisation to third objective disease progression or death from any cause (whichever comes first). If a patient started second subsequent treatment before disease progression, then the first objective disease progression prior to the start of third subsequent treatment was considered as event. PFS3 was assessed in follow-up period.	
End point type	Secondary
End point timeframe: From date of randomisation to end of follow-up.	

End point values	Resminostat - ITT	Placebo - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: months				
median (confidence interval 95%)	37.6 (24.9 to 67.5)	45.5 (32.3 to 59.7)		

Statistical analyses

Statistical analysis title	Analysis of the Secondary Endpoint PFS3
Statistical analysis description:	
A two-sided stratified log-rank test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Hazard Ratio from a Cox Proportional Hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as strata.	
Comparison groups	Resminostat - ITT v Placebo - ITT
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.921
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.674
upper limit	1.547

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent form up to completion of the 30th day after the last administration of trial drug.

Adverse event reporting additional description:

Only treatment-emergent adverse events are shown here.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Resminostat
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Reporting group description:

Subjects who were treated with resminostat during the randomized or rollover period.

This includes patients randomized to resminostat (N=100) and patients randomized to placebo who rolled over to open-label treatment with resminostat (N=80).

Reporting group title	Placebo
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Reporting group description:

Subjects who received placebo during the randomised period.

Serious adverse events	Resminostat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 180 (18.33%)	12 / 101 (11.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders	Deep vein thrombosis			
	subjects affected / exposed	1 / 180 (0.56%)	1 / 101 (0.99%)	
	occurrences causally related to treatment / all	1 / 1	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion	subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions	Impaired healing			
	subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness	subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
	occurrences causally related to treatment / all	0 / 0	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema	Additional description: Reported during the rollover period (i.e. after unblinding).			
	subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Reported during the rollover period (i.e. after unblinding).			
	subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Reported during the rollover period (i.e. after unblinding).			
	subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
	occurrences causally related to treatment / all	0 / 2	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling	Additional description: Reported during the rollover period (i.e. after unblinding).			

subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: One SAE in the resminostat group was reported during the rollover period (open label).		
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased	Additional description: One SAE was reported during the rollover period (open label).		
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased	Additional description: One SAE was reported during the rollover period (open label).		

subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial infarction	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy	Additional description: One SAE in the resminostat group was reported during the rollover period (open label).		
subjects affected / exposed	2 / 180 (1.11%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ectropion			

subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain of skin	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin burning sensation			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: One SAE in the resminostat group was reported during the rollover period (open-label).		
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			

subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: One SAE in the resminostat group was reported during the rollover period (open label).		
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis	Additional description: One SAE in the resminostat group was reported during the rollover period (open label).		
subjects affected / exposed	3 / 180 (1.67%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			

subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: SAE in the resminostat group reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 180 (1.11%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: SAE in the resminostat group was reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe acute respiratory syndrome	Additional description: SAE in the resminostat group was reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection	Additional description: Reported during the rollover period (i.e. after unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia	Additional description: Reported during the rollover period (i.e. after unblinding).		

	unblinding).		
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 180 (0.56%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Resminostat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 180 (95.56%)	81 / 101 (80.20%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 180 (7.22%)	8 / 101 (7.92%)	
occurrences (all)	30	9	
Flushing			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	12	1	
Hot flush			
subjects affected / exposed	4 / 180 (2.22%)	0 / 101 (0.00%)	
occurrences (all)	5	0	
Hypotension			

subjects affected / exposed occurrences (all)	5 / 180 (2.78%) 17	0 / 101 (0.00%) 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 180 (10.00%)	4 / 101 (3.96%)	
occurrences (all)	30	4	
Chills			
subjects affected / exposed	10 / 180 (5.56%)	1 / 101 (0.99%)	
occurrences (all)	15	1	
Fatigue			
subjects affected / exposed	60 / 180 (33.33%)	15 / 101 (14.85%)	
occurrences (all)	119	40	
Influenza like illness			
subjects affected / exposed	14 / 180 (7.78%)	6 / 101 (5.94%)	
occurrences (all)	24	12	
Oedema peripheral			
subjects affected / exposed	9 / 180 (5.00%)	5 / 101 (4.95%)	
occurrences (all)	10	5	
Pyrexia			
subjects affected / exposed	16 / 180 (8.89%)	8 / 101 (7.92%)	
occurrences (all)	22	8	
Malaise			
subjects affected / exposed	10 / 180 (5.56%)	0 / 101 (0.00%)	
occurrences (all)	21	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 180 (8.33%)	6 / 101 (5.94%)	
occurrences (all)	16	6	
Dyspnoea			
subjects affected / exposed	9 / 180 (5.00%)	4 / 101 (3.96%)	
occurrences (all)	18	5	
Oropharyngeal pain			
subjects affected / exposed	6 / 180 (3.33%)	2 / 101 (1.98%)	
occurrences (all)	7	2	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	32 / 180 (17.78%)	4 / 101 (3.96%)	
occurrences (all)	53	5	
Hallucination			
subjects affected / exposed	5 / 180 (2.78%)	0 / 101 (0.00%)	
occurrences (all)	6	0	
Depression			
subjects affected / exposed	3 / 180 (1.67%)	3 / 101 (2.97%)	
occurrences (all)	3	3	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	17 / 180 (9.44%)	2 / 101 (1.98%)	
occurrences (all)	20	2	
Blood creatinine increased			
subjects affected / exposed	17 / 180 (9.44%)	2 / 101 (1.98%)	
occurrences (all)	23	2	
Neutrophil count decreased			
subjects affected / exposed	9 / 180 (5.00%)	1 / 101 (0.99%)	
occurrences (all)	58	1	
Platelet count decreased			
subjects affected / exposed	12 / 180 (6.67%)	0 / 101 (0.00%)	
occurrences (all)	16	0	
Weight decreased			
subjects affected / exposed	10 / 180 (5.56%)	2 / 101 (1.98%)	
occurrences (all)	10	2	
White blood cell count decreased			
subjects affected / exposed	10 / 180 (5.56%)	1 / 101 (0.99%)	
occurrences (all)	39	3	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 180 (3.33%)	3 / 101 (2.97%)	
occurrences (all)	9	3	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 180 (3.33%)	3 / 101 (2.97%)	
occurrences (all)	12	3	
Lymphocyte count decreased			

subjects affected / exposed occurrences (all)	7 / 180 (3.89%) 10	3 / 101 (2.97%) 4	
Monocyte count increased subjects affected / exposed occurrences (all)	5 / 180 (2.78%) 6	0 / 101 (0.00%) 0	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	4 / 180 (2.22%) 4	2 / 101 (1.98%) 3	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	4 / 180 (2.22%) 4	1 / 101 (0.99%) 1	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	7 / 180 (3.89%) 9	0 / 101 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	15 / 180 (8.33%) 18	3 / 101 (2.97%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	46 / 180 (25.56%) 167	2 / 101 (1.98%) 2	
Headache subjects affected / exposed occurrences (all)	31 / 180 (17.22%) 103	10 / 101 (9.90%) 12	
Paraesthesia subjects affected / exposed occurrences (all)	10 / 180 (5.56%) 12	3 / 101 (2.97%) 3	
Tremor subjects affected / exposed occurrences (all)	4 / 180 (2.22%) 6	0 / 101 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	10 / 180 (5.56%) 13	4 / 101 (3.96%) 4	

Neutropenia			
subjects affected / exposed	9 / 180 (5.00%)	0 / 101 (0.00%)	
occurrences (all)	24	0	
Thrombocytopenia			
subjects affected / exposed	7 / 180 (3.89%)	1 / 101 (0.99%)	
occurrences (all)	12	2	
Monocytosis			
subjects affected / exposed	4 / 180 (2.22%)	0 / 101 (0.00%)	
occurrences (all)	8	0	
Lymphadenopathy			
subjects affected / exposed	2 / 180 (1.11%)	3 / 101 (2.97%)	
occurrences (all)	3	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	7 / 180 (3.89%)	2 / 101 (1.98%)	
occurrences (all)	10	6	
Eye disorders			
Dry eye			
subjects affected / exposed	6 / 180 (3.33%)	1 / 101 (0.99%)	
occurrences (all)	6	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 180 (11.11%)	1 / 101 (0.99%)	
occurrences (all)	25	1	
Abdominal pain upper			
subjects affected / exposed	23 / 180 (12.78%)	5 / 101 (4.95%)	
occurrences (all)	61	5	
Constipation			
subjects affected / exposed	15 / 180 (8.33%)	5 / 101 (4.95%)	
occurrences (all)	18	6	
Diarrhoea			
subjects affected / exposed	75 / 180 (41.67%)	17 / 101 (16.83%)	
occurrences (all)	264	19	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 180 (5.56%)	1 / 101 (0.99%)	
occurrences (all)	11	1	
Nausea			

subjects affected / exposed	120 / 180 (66.67%)	10 / 101 (9.90%)	
occurrences (all)	414	11	
Vomiting			
subjects affected / exposed	59 / 180 (32.78%)	3 / 101 (2.97%)	
occurrences (all)	120	3	
Dyspepsia			
subjects affected / exposed	10 / 180 (5.56%)	3 / 101 (2.97%)	
occurrences (all)	11	3	
Dry mouth			
subjects affected / exposed	6 / 180 (3.33%)	0 / 101 (0.00%)	
occurrences (all)	25	0	
Toothache			
subjects affected / exposed	6 / 180 (3.33%)	3 / 101 (2.97%)	
occurrences (all)	6	3	
Abdominal distension			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	7	1	
Gastritis			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	4	1	
Stomatitis			
subjects affected / exposed	5 / 180 (2.78%)	1 / 101 (0.99%)	
occurrences (all)	7	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 180 (7.78%)	2 / 101 (1.98%)	
occurrences (all)	15	2	
Pruritus			
subjects affected / exposed	24 / 180 (13.33%)	13 / 101 (12.87%)	
occurrences (all)	28	19	
Rash			
subjects affected / exposed	10 / 180 (5.56%)	2 / 101 (1.98%)	
occurrences (all)	19	2	
Dry skin			
subjects affected / exposed	7 / 180 (3.89%)	2 / 101 (1.98%)	
occurrences (all)	7	2	

Dermatitis acneiform subjects affected / exposed occurrences (all)	4 / 180 (2.22%) 5	1 / 101 (0.99%) 1	
Erythema subjects affected / exposed occurrences (all)	5 / 180 (2.78%) 5	1 / 101 (0.99%) 1	
Skin ulcer subjects affected / exposed occurrences (all)	5 / 180 (2.78%) 6	0 / 101 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	3 / 180 (1.67%) 3	4 / 101 (3.96%) 4	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	15 / 180 (8.33%) 17	6 / 101 (5.94%) 6	
Back pain subjects affected / exposed occurrences (all)	13 / 180 (7.22%) 23	8 / 101 (7.92%) 10	
Muscle spasms subjects affected / exposed occurrences (all)	36 / 180 (20.00%) 52	5 / 101 (4.95%) 8	
Myalgia subjects affected / exposed occurrences (all)	14 / 180 (7.78%) 16	1 / 101 (0.99%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	15 / 180 (8.33%) 16	1 / 101 (0.99%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	6 / 180 (3.33%) 6	4 / 101 (3.96%) 4	
Infections and infestations Corona virus infection subjects affected / exposed occurrences (all)	11 / 180 (6.11%) 11	6 / 101 (5.94%) 6	
Nasopharyngitis			

subjects affected / exposed	21 / 180 (11.67%)	17 / 101 (16.83%)	
occurrences (all)	29	22	
Influenza			
subjects affected / exposed	8 / 180 (4.44%)	0 / 101 (0.00%)	
occurrences (all)	10	0	
Skin infection			
subjects affected / exposed	7 / 180 (3.89%)	1 / 101 (0.99%)	
occurrences (all)	8	1	
Upper respiratory tract infection			
subjects affected / exposed	8 / 180 (4.44%)	2 / 101 (1.98%)	
occurrences (all)	13	2	
Bronchitis			
subjects affected / exposed	5 / 180 (2.78%)	4 / 101 (3.96%)	
occurrences (all)	7	4	
Folliculitis			
subjects affected / exposed	4 / 180 (2.22%)	2 / 101 (1.98%)	
occurrences (all)	4	2	
Sinusitis			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	5	1	
Tinea pedis			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	4	1	
Urinary tract infection			
subjects affected / exposed	4 / 180 (2.22%)	3 / 101 (2.97%)	
occurrences (all)	4	4	
Pharyngitis			
subjects affected / exposed	0 / 180 (0.00%)	3 / 101 (2.97%)	
occurrences (all)	0	3	
Rhinitis			
subjects affected / exposed	3 / 180 (1.67%)	3 / 101 (2.97%)	
occurrences (all)	3	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 180 (20.56%)	2 / 101 (1.98%)	
occurrences (all)	64	2	

Hyperuricaemia			
subjects affected / exposed	4 / 180 (2.22%)	4 / 101 (3.96%)	
occurrences (all)	4	4	
Hypokalaemia			
subjects affected / exposed	4 / 180 (2.22%)	1 / 101 (0.99%)	
occurrences (all)	6	1	
Hyperglycaemia			
subjects affected / exposed	2 / 180 (1.11%)	3 / 101 (2.97%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2016	The changes introduced by this Amendment (Protocol Version 2.0) were made to add the definition of abstinence from heterosexual intercourse (inclusion criteria #6, Protocol Section 16.6.1 contraception), clarify the process for emergency unblinding, clarify submission and approval of substantial amendments to the competent regulatory authorities and correct minor typos in the Schedule of Assessments.
24 October 2016	The changes introduced by this Amendment (Protocol Version 3.0) were made to include changes in the accepted contraceptive measures, to specify the use of highly effective contraceptive measures according to the Clinical Trials Facilitation and Coordination Group (CTFG) Guideline and to add serum pregnancy tests every other cycle starting from Cycle 3.
09 March 2017	This Amendment (Protocol Version 4.0) incorporated the changes of the previous two Amendments for all participating countries. In addition, it clarified the response assessment of skin disease (adaptation of the GRS, Olsen et al 2011) and the prior therapy qualifying for inclusion criterion #1, modified the allowed window between completion of prior treatment and randomization (from 8 weeks to 12 weeks), added evaluation of changes in the VAS itching score and updated the new address of the sponsor. Furthermore, the amendment clarified that serum pregnancy tests were mandatory only at screening and EOT; at all other visits requiring pregnancy testing, test in serum or urine was allowed.
23 July 2018	The changes introduced by this Amendment (Protocol Version 5.0) were made to update information regarding clinical trials with resminostat, clarify the disease stage used for stratification, modify exclusion criterion #8 (history of prior cancers), add systemic steroids as anti-itching medication to the list of prohibited medication (also restricted for other indications), clarify and modify the procedures for rollover, clarify response assessments, modify the requirements to start a new treatment cycle (alignment with toxicity guidelines, administration of trial medication before safety laboratory results are available), allow reescalation of the dose to 600 mg/day if the dose was reduced due to nausea, vomiting or similar gastrointestinal events, remove Chief Development Officer from list of sponsor signatories and correct minor inconsistencies and typos.
28 February 2019	<p>The changes introduced by this Amendment (Protocol Version 6.0) were made to recalculate the sample size based on the observed patient dropout rate of up to 30% (prior assumption: 10%). The number of patients required to observe 125 PFS events was increased to 95 patients per treatment arm (total number of patients: 190). Furthermore, the changes introduced by Amendment No. 4 concerning requirements to start a new treatment cycle were updated in several other sections of the protocol.</p> <p>A Protocol Version 6.1 (applicable in Germany only) was set up at the request of the German regulatory authority (Bundesministerium fuer Arzneimittel und Medizinprodukte, BfArM) to reinstall the requirement to check safety laboratory analyses on Day 1 of each new treatment cycle before administration of trial medication.</p> <p>An Addendum (Protocol Version 6.2; applicable in Belgium only) was set up based on concerns of the IEC in Belgium that patients with progressing tumors not meeting the defined criteria for PD could stay on trial treatment although a different treatment would be warranted. Therefore, exclusion criterion #15 was added to exclude patients with tumoral stage MF lacking involvement of the skin.</p>

15 November 2021	The changes introduced by this Amendment (Protocol Version 7.0) were made to recalculate the sample size based on the observed patient dropout rate of 33% (prior assumption: up to 30%). The number of patients required to observe 125 PFS events for the main data analysis was increased to 100 patients per treatment arm (total number of patients: 200). In case 125 events were not reached upon randomization of 200 patients, the main analysis had to be performed 10 months after randomization of the last patient. Furthermore, patients on CR, PR or SD and without any AE of Grade ≥ 2 or any AE considered clinically relevant and related to trial medication during the last 6 cycles were allowed to skip site visits scheduled between the visits of intermediate and complete response assessments. The same changes were introduced to the current protocol in Germany (leading to Protocol Version 7.1) and Belgium (leading to Protocol Version 7.2).
21 December 2022	The changes introduced by this Amendment (Protocol Version 8.0) were made to specify communication of trial results (primary endpoint) to participating investigators and patients upon the main statistical data analysis. Accordingly, participants were to be informed of their treatment allocation (unblinding). In case of positive results, patients on placebo were to be offered to roll-over to resminostat therapy and patients on resminostat could continue openlabel treatment with resminostat. In case of negative results, all patients were to be discontinued from trial treatment and the trial was to be terminated. Furthermore, performance of skin biopsy and blood sampling for biomarkers and PK were no longer required. The same changes were introduced to the current protocol in Germany (leading to Protocol Version 8.1) and Belgium (leading to Protocol Version 8.2).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported