



Clinical trial results:

A Two-Part Study to Assess the Safety and Preliminary Efficacy of Givinostat in Patients with JAK2V617F Positive Polycythemia Vera Summary

EudraCT number	2013-000860-27
Trial protocol	IT FR DE GB PL HU
Global end of trial date	25 September 2017

Results information

Result version number	v1 (current)
This version publication date	25 January 2019
First version publication date	25 January 2019

Trial information

Trial identification

Sponsor protocol code	DSC/12/2357/45
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01901432
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ITALFARMACO S.p.A.
Sponsor organisation address	Via dei Laboratori, 54, Cinisello Balsamo (MI), Italy, 20092
Public contact	Medical Expert, ITALFARMACO S.p.A., 39 026443 258, p.bettica@italfarmaco.com
Scientific contact	Medical Expert, ITALFARMACO S.p.A., 39 026443 258, p.bettica@italfarmaco.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	25 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2017
Global end of trial reached?	Yes
Global end of trial date	25 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A

- To characterize the safety, tolerability and maximum tolerated dose (MTD) of givinostat in patients with Polycythemia Vera (PV).

Part B

- To evaluate the preliminary efficacy of givinostat at the MTD after 3 cycles.
- To determine the safety and tolerability of givinostat at the MTD after 3 cycles.

In Part A, all patients were to receive givinostat at an initial dose level (DL) of 100 milligrams (mg) twice daily (b.i.d.). In Part B, patients were to receive givinostat at the MTD determined in Part A.

Protection of trial subjects:

The Investigator ensured that this study was conducted in full conformity with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonisation Tripartite Guideline or with local law if it afforded greater protection to the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
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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)	35
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 2-part, multisite, open-label, non-randomized study to assess givinostat in patients with JAK2^{V617F} positive PV. Part A assessed safety and was the dose escalation portion of study, while Part B assessed preliminary efficacy. Patients were enrolled in 5 countries (France, Germany, Italy, Poland and the United Kingdom).

Pre-assignment

Screening details:

Patients were enrolled into either Part A or Part B, transition from 1 part to the other was not allowed. 48 patients were enrolled into the study overall: 12 patients in Part A to determine the MTD and 36 patients in Part B.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Givinostat DL0 (50 mg b.i.d.) (Part A)

Arm description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at Dose Level 0 (DL0) (50 milligrams [mg] b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Patients were treated for up to 6 cycles (28 days in each cycle).

There were 3 DLs used during Part A; 50 mg b.i.d. (DL0) was the third DL to be administered.

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	Givinostat (ITF2357)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The product was supplied as hard gelatine capsules for oral administration at the strength of 50 mg, 75 mg and/or 100 mg each.

In Part A, patients were assigned to receive the following DLs, progressively used:

- DL1 (100 mg b.i.d.);
- DL6 (2 capsules of 50 mg in the morning, AND one capsule of 50 mg in the evening);
- DL0 (50 mg b.i.d.).

Arm title	Givinostat DL1 (100 mg b.i.d.) (Part A)
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Arm description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL1 (100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.

Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	Givinostat (ITF2357)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The product was supplied as hard gelatine capsules for oral administration at the strength of 50 mg, 75 mg and/or 100 mg each.

In Part A, patients were assigned to receive the following DLs, progressively used:

- DL1 (100 mg b.i.d.);
- DL6 (2 capsules of 50 mg in the morning, AND one capsule of 50 mg in the evening);
- DL0 (50 mg b.i.d.).

In Part B, the starting dose of givinostat was the MTD determined in Part A (i.e. 100 mg b.i.d.).

Arm title	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Arm description: Following initial assignment of 3 patients to DL1 in Part A, a further 3 patients were assigned to DL1 so this treatment group is referred to as "DL1 expanded" (patients received givinostat by oral administration at 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.	
Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	Givinostat (ITF2357)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The product was supplied as hard gelatine capsules for oral administration at the strength of 50 mg, 75 mg and/or 100 mg each.

In Part A, patients were assigned to receive the following DLs, progressively used:

- DL1 (100 mg b.i.d.);
- DL6 (2 capsules of 50 mg in the morning, AND one capsule of 50 mg in the evening);
- DL0 (50 mg b.i.d.).

In Part B, the starting dose of givinostat was the MTD determined in Part A (i.e. 100 mg b.i.d.).

Arm title	Givinostat DL6 (100 mg + 50 mg) (Part A)
Arm description: In Part A, 3 patients were assigned to receive givinostat by oral administration at DL6 (100 mg in the morning and 50 mg in the evening, i.e. 12 hours after). Patients were treated for up to 6 cycles in (28 days in each cycle). There were 3 DLs used during Part A; 100 mg + 50 mg (DL6) was the second DL to be administered.	
Arm type	Experimental
Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	Givinostat (ITF2357)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The product was supplied as hard gelatine capsules for oral administration at the strength of 50 mg, 75 mg and/or 100 mg each.

In Part A, patients were assigned to receive the following DLs, progressively used:

- DL1 (100 mg b.i.d.);
- DL6 (2 capsules of 50 mg in the morning, AND one capsule of 50 mg in the evening);
- DL0 (50 mg b.i.d.).

In Part B, the starting dose of givinostat was the MTD determined in Part A (i.e. 100 mg b.i.d.).

Arm title	Givinostat at MTD (100 mg b.i.d.) (Part B)
Arm description: In Part B, patients were assigned to receive the starting dose of givinostat by oral administration at the MTD determined in Part A (i.e. 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Based on evaluations performed as part of the visit procedures on Day 28 of each cycle up to Cycle 5 and/or in any necessary additional study visit, the givinostat dose was decreased if appropriate for any patients that met dose reduction criteria.	
Arm type	Experimental

Investigational medicinal product name	Givinostat
Investigational medicinal product code	
Other name	Givinostat (ITF2357)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The product was supplied as hard gelatine capsules for oral administration at the strength of 50 mg, 75 mg and/or 100 mg each.

In Part B, the starting dose was the MTD determined in Part A, therefore all patients received givinostat at 100 mg b.i.d. during Cycle 1. During Part B Cycle 2 givinostat was administered at 100 mg, 75 mg and 50 mg b.i.d., since dose reductions were allowed from Cycle 2 onwards, as per protocol.

Number of subjects in period 1	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Started	3	3	3
Received study drug	3	3	3
Completed	3	2	1
Not completed	0	1	2
Patient decision to stop study drug	-	-	-
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Adverse event, non-fatal	-	1	1

Number of subjects in period 1	Givinostat DL6 (100 mg + 50 mg) (Part A)	Givinostat at MTD (100 mg b.i.d.) (Part B)
Started	3	36
Received study drug	3	35
Completed	3	27
Not completed	0	9
Patient decision to stop study drug	-	1
Consent withdrawn by subject	-	5
Physician decision	-	2
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Givinostat DL0 (50 mg b.i.d.) (Part A)
Reporting group description:	
In Part A, 3 patients were assigned to receive givinostat by oral administration at Dose Level 0 (DL0) (50 milligrams [mg] b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Patients were treated for up to 6 cycles (28 days in each cycle). There were 3 DLs used during Part A; 50 mg b.i.d. (DL0) was the third DL to be administered.	
Reporting group title	Givinostat DL1 (100 mg b.i.d.) (Part A)
Reporting group description:	
In Part A, 3 patients were assigned to receive givinostat by oral administration at DL1 (100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.	
Reporting group title	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Reporting group description:	
Following initial assignment of 3 patients to DL1 in Part A, a further 3 patients were assigned to DL1 so this treatment group is referred to as "DL1 expanded" (patients received givinostat by oral administration at 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.	
Reporting group title	Givinostat DL6 (100 mg + 50 mg) (Part A)
Reporting group description:	
In Part A, 3 patients were assigned to receive givinostat by oral administration at DL6 (100 mg in the morning and 50 mg in the evening, i.e. 12 hours after). Patients were treated for up to 6 cycles in (28 days in each cycle). There were 3 DLs used during Part A; 100 mg + 50 mg (DL6) was the second DL to be administered.	
Reporting group title	Givinostat at MTD (100 mg b.i.d.) (Part B)
Reporting group description:	
In Part B, patients were assigned to receive the starting dose of givinostat by oral administration at the MTD determined in Part A (i.e. 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Based on evaluations performed as part of the visit procedures on Day 28 of each cycle up to Cycle 5 and/or in any necessary additional study visit, the givinostat dose was decreased if appropriate for any patients that met dose reduction criteria.	

Reporting group values	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Number of subjects	3	3	3
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	2	1
From 65-84 years	1	1	2
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	2	1	1
Male	1	2	2

Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	3	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Givinostat DL6 (100 mg + 50 mg) (Part A)	Givinostat at MTD (100 mg b.i.d.) (Part B)	Total
Number of subjects	3	36	48
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	28	35
From 65-84 years	1	8	13
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	1	11	16
Male	2	25	32
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	36	48
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Givinostat DL0 (50 mg b.i.d.) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at Dose Level 0 (DL0) (50 milligrams [mg] b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Patients were treated for up to 6 cycles (28 days in each cycle).

There were 3 DLs used during Part A; 50 mg b.i.d. (DL0) was the third DL to be administered.

Reporting group title	Givinostat DL1 (100 mg b.i.d.) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL1 (100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.

Reporting group title	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
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Reporting group description:

Following initial assignment of 3 patients to DL1 in Part A, a further 3 patients were assigned to DL1 so this treatment group is referred to as "DL1 expanded" (patients received givinostat by oral administration at 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

There were 3 DLs used during Part A; 100 mg b.i.d. (DL1) was the initial DL to be administered.

Reporting group title	Givinostat DL6 (100 mg + 50 mg) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL6 (100 mg in the morning and 50 mg in the evening, i.e. 12 hours after). Patients were treated for up to 6 cycles in (28 days in each cycle).

There were 3 DLs used during Part A; 100 mg + 50 mg (DL6) was the second DL to be administered.

Reporting group title	Givinostat at MTD (100 mg b.i.d.) (Part B)
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Reporting group description:

In Part B, patients were assigned to receive the starting dose of givinostat by oral administration at the MTD determined in Part A (i.e. 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Based on evaluations performed as part of the visit procedures on Day 28 of each cycle up to Cycle 5 and/or in any necessary additional study visit, the givinostat dose was decreased if appropriate for any patients that met dose reduction criteria.

Subject analysis set title	Givinostat Total (Part A)
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

This dataset comprised all patients in the Intent-to-Treat (ITT) analysis set who received givinostat in Part A of the study. It represents the 4 Part A treatment arms and includes patients who received givinostat at DL0 (50 mg b.i.d.), DL1 (100 mg b.i.d. [i.e. including DL1 expanded] and DL6 (100 mg + 50 mg) in Part A.

The ITT analysis set included all recruited patients who received 1 dose of study drug and from whom 1 post-baseline efficacy measurement was obtained.

Subject analysis set title	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for pharmacokinetic (PK) analysis and included the patients who received givinostat at DL0 (50 mg b.i.d.) in Part A of the study and for whom PK data was available for analysis.

Subject analysis set title	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for PK analysis and included the patients who received givinostat at DL1 (100 mg b.i.d. [i.e. including DL1 expanded]) in Part A of the study and for whom PK data was available for analysis.

Subject analysis set title	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for PK analysis and included the patients who received givinostat at DL6 (100 mg

in the morning and 50 mg in the evening) in Part A of the study and for whom PK data was available for analysis.

Subject analysis set title	Givinostat 100 mg b.i.d. (Part B PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for PK analysis and included patients who received givinostat at the MTD (100 mg b.i.d.) in Part B of the study and for whom PK data was available for analysis. This dataset was used for PK analysis after Cycle 1 Day 1 (34 patients) and after Cycle 2 Day 28 (17 patients remaining at this dose).

Subject analysis set title	Givinostat 75 mg b.i.d. (Part B PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for PK analysis and included patients who received givinostat at the reduced dose of 75 mg b.i.d. in Part B of the study and for whom PK data was available for analysis. This dataset only applied for PK analysis from Cycle 2 onwards (i.e. Cycle 2 Day 28).

Subject analysis set title	Givinostat 50 mg b.i.d. (Part B PK analysis set)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

This dataset was used for PK analysis and included patients who received givinostat at the reduced dose of 50 mg b.i.d. in Part B of the study and for whom PK data was available for analysis. This dataset only applied for PK analysis from Cycle 2 onwards (i.e. Cycle 2 Day 28).

Primary: Number of Patients Experiencing Treatment-emergent Adverse Events (TEAEs) in Part A of the Study

End point title	Number of Patients Experiencing Treatment-emergent Adverse Events (TEAEs) in Part A of the Study ^{[1][2]}
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End point description:

Evaluations were performed on the type, incidence and severity of TEAEs, graded according to Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03, following administration of givinostat for up to 6 cycles of treatment in Part A. Grades 1 through 5 were as follows: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe or medically significant but not immediately life threatening or requiring hospitalisation; Grade 4: Life threatening consequences; Grade 5: Death related to AE. Results are reported as number of patients with TEAEs for each of the indicated categories. Definitions: drug-related TEAE / treatment-emergent serious adverse event (TESAE) corresponded to reasonable suspicion that the TEAE / TESAE was associated with the use of the study drug, according to investigator assessment; discontinuation refers to discontinuation from treatment. Analysis performed on the Safety (SAF) analysis set, comprising all recruited patients who received 1 dose of study drug.

End point type	Primary
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End point timeframe:

168 days (up to Cycle 6 Day 28 in Part A).

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: Only descriptive analyses were performed as planned.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The treatment arm 'Givinostat at MTD (100 mg b.i.d.) (Part B)' is not applicable for this end point as only Part A study results are being presented.

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)	Givinostat DL6 (100 mg + 50 mg) (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: participants				
TEAE	3	3	3	3
Drug-related TEAE	1	3	3	1
TESAE	0	1	0	1

Drug-related TESAE	0	0	0	0
Death due to any cause	0	0	0	0
Grade 3 TEAE	0	2	1	1
Grade 3 drug-related TEAE	0	2	1	0
Grade 4 TEAE	0	0	1	0
Grade 4 drug-related TEAE	0	0	1	0
Grade 5 TEAE	0	0	0	0
Discontinuation due to TEAE	0	1	1	0
Discontinuation due to drug-related TEAE	0	1	1	0
Discontinuation due to TESAE	0	0	0	0
Discontinuation due to drug-related TESAE	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Dose Limiting Toxicities (DLTs) After 1 Cycle in Part A of the Study

End point title	Dose Limiting Toxicities (DLTs) After 1 Cycle in Part A of the Study ^{[3][4]}
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End point description:

The MTD of givinostat was based only on Cycle 1 DLTs. A DLT was defined as the following drug-related toxicity:

- Grade 4 hematological toxicity, or
- Grade 3 febrile neutropenia, or
- Grade ≥3 non-hematological toxicity (with the exception Grade 3 diarrhea without adequate supportive care lasting less than 3 days, and Grade 3 nausea or vomiting without adequate supportive care lasting less than 3 days), or
- Any drug-related serious AE, or
- Any toxicity clearly not related to disease progression or intercurrent illness requiring interruption of dosing for more than 3 days during first cycle.

At end of Cycle 1, for the third patient in each DL, the safety of the 3 patients treated for 1 cycle was reviewed and it was decided if the dose should be escalated or not. Results are reported as the number of patients with DLT events for Cycle 1 in Part A. Analysis performed on MTD analysis set, comprising all patients who experienced a DLT or received ≥90% of study drug doses in Cycle 1.

End point type	Primary
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End point timeframe:

28 days (up to Cycle 1 Day 28 in Part A).

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: Only descriptive analyses were performed as planned.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The treatment arm 'Givinostat at MTD (100 mg b.i.d.) (Part B)' is not applicable for this end point as only Part A study results are being presented.

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)	Givinostat DL6 (100 mg + 50 mg) (Part A)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: participants	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients Experiencing TEAEs After 3 Cycles in Part B of the Study

End point title	Number of Patients Experiencing TEAEs After 3 Cycles in Part B of the Study ^[5] ^[6]
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End point description:

Evaluations were performed on the type, incidence and severity of TEAEs, graded according to CTCAE v. 4.03, following administration of givinostat at the MTD for up to 3 cycles of treatment in Part B. Grades 1 through 5 were as follows: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe or medically significant but not immediately life threatening or requiring hospitalisation; Grade 4: Life threatening consequences; Grade 5: Death related to AE. Results are reported as number of patients with TEAEs for each of the indicated categories. Definitions: drug-related TEAE / TESAE corresponded to reasonable suspicion that the TEAE / TESAE was associated with the use of the study drug, according to investigator assessment; discontinuation refers to discontinuation from treatment. Analysis performed on the SAF analysis set.

End point type	Primary
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End point timeframe:

84 days (up to Cycle 3 Day 28 in Part B).

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: Only descriptive analyses were performed as planned.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The treatment arms 'Givinostat DL0 (50 mg b.i.d.) (Part A)', 'Givinostat DL1 (100 mg b.i.d.) (Part A)', 'Givinostat DL1 expanded (100 mg b.i.d.) (Part A)' and 'Givinostat DL6 (100 mg + 50 mg) (Part A)' are not applicable for this end point as only Part B study results are being presented.

End point values	Givinostat at MTD (100 mg b.i.d.) (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: participants				
TEAE	35			
Drug-related TEAE	33			
TESAE	2			
Drug-related TESAE	1			
Death due to any cause	0			
Grade 3 TEAE	10			
Grade 3 drug-related TEAE	7			
Grade 4 TEAE	0			
Grade 4 drug-related TEAE	0			
Grade 5 TEAE	0			
Discontinuation due to TEAE	2			

Discontinuation due to drug-related TEAE	2			
Discontinuation due to TESAE	0			
Discontinuation due to drug-related TESAE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) (i.e. Complete Response [CR] and Partial Response [PR]) After 3 Cycles in Part B of the Study

End point title	Overall Response Rate (ORR) (i.e. Complete Response [CR] and Partial Response [PR]) After 3 Cycles in Part B of the Study ^{[7][8]}
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End point description:

ORR, CR and PR following administration of givinostat at MTD for 3 cycles in Part B, reported as percentage of patients with a response. Response was evaluated according to the clinico-hematological European LeukemiaNet (ELN) response criteria. If Investigator's clinical response assessment (taking into account the overall medical judgment of the specific patient's case) was not in agreement with exact application of the ELN response criteria, the Investigator's assessment superseded the mathematical application of these criteria and was used for analysis. Analysis performed on ITT analysis set.

CR defined as:

- 1.Hematocrit (HCT) <45% without phlebotomy, and
- 2.Platelets $\leq 400 \times 10^9/\text{litre (L)}$, and
- 3.White Blood Cell count $\leq 10 \times 10^9/\text{L}$, and
- 4.Normal spleen size, and
- 5.No disease-related systemic symptoms (i.e. pruritus, headache, microvascular disturbances).

PR defined as: Patients not fulfilling CR and

- 1.HCT <45% without phlebotomy, or
- 2.Response in ≥ 3 other criteria.

End point type	Primary
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End point timeframe:

84 days (up to cycle 3 Day 28 in Part B).

Notes:

[7] - 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: Only descriptive analyses were performed as planned.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The treatment arms 'Givinostat DL0 (50 mg b.i.d.) (Part A)', 'Givinostat DL1 (100 mg b.i.d.) (Part A)', 'Givinostat DL1 expanded (100 mg b.i.d.) (Part A)' and 'Givinostat DL6 (100 mg + 50 mg) (Part A)' are not applicable for this end point as only Part B study results are being presented.

End point values	Givinostat at MTD (100 mg b.i.d.) (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percentage of participants				
number (confidence interval 95%)				
ORR (CR + PR)	80.6 (62.53 to 92.55)			
CR	9.7 (2.04 to 25.75)			

PR	71.0 (51.96 to 85.78)			
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Statistical analyses

No statistical analyses for this end point

Secondary: ORR After 3 Cycles and After 6 Cycles in Part A of the Study

End point title	ORR After 3 Cycles and After 6 Cycles in Part A of the Study
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End point description:

ORR following administration of givinostat after 3 cycles and after 6 cycles in Part A, reported as percentage of patients with a response. Response was evaluated according to the clinico-hematological ELN response criteria. If Investigator's clinical response assessment (taking into account the overall medical judgment of the specific patient's case) was not in agreement with exact application of the ELN response criteria, the Investigator's assessment superseded the mathematical application of these criteria and was used for analysis. Analysis performed on ITT analysis set using the dataset for all Part A patients combined.

End point type	Secondary
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End point timeframe:

84 and 168 days (up to Cycle 3 Day 28 and Cycle 6 Day 28 in Part A).

End point values	Givinostat Total (Part A)			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 3 Day 28	72.7 (39.03 to 93.98)			
Cycle 6 Day 28	72.7 (39.03 to 93.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR After 6 Cycles in Part B of the Study

End point title	ORR After 6 Cycles in Part B of the Study ^[9]
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End point description:

ORR following administration of givinostat at the MTD for 6 cycles in Part B, reported as percentage of patients with a response. Response was evaluated according to the clinico-hematological ELN response criteria. If Investigator's clinical response assessment (taking into account the overall medical judgment of the specific patient's case) was not in agreement with exact application of the ELN response criteria, the Investigator's assessment superseded the mathematical application of these criteria and was used for analysis. Analysis performed on ITT analysis set.

End point type	Secondary
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End point timeframe:

168 days (up to Cycle 6 Day 28 in Part B).

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The treatment arms 'Givinostat DL0 (50 mg b.i.d.) (Part A)', 'Givinostat DL1 (100 mg b.i.d.) (Part A)', 'Givinostat DL1 expanded (100 mg b.i.d.) (Part A)' and 'Givinostat DL6 (100 mg + 50 mg) (Part A)' are not applicable for this end point as only Part B study results are being presented.

End point values	Givinostat at MTD (100 mg b.i.d.) (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percentage of participants				
number (confidence interval 95%)	80.6 (62.53 to 92.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Experiencing TEAEs After 6 Cycles in Part B of the Study

End point title	Number of Patients Experiencing TEAEs After 6 Cycles in Part B of the Study ^[10]
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End point description:

Evaluations were performed on the type, incidence and severity of TEAEs, graded according to CTCAE v. 4.03, following administration of givinostat at the MTD for up to 6 cycles of treatment in Part B. Grades 1 through 5 were as follows: Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe or medically significant but not immediately life threatening or requiring hospitalisation; Grade 4: Life threatening consequences; Grade 5: Death related to AE. Results are reported as number of patients with TEAEs for each of the indicated categories. Definitions: drug-related TEAE / TESAE corresponded to reasonable suspicion that the TEAE / TESAE was associated with the use of the study drug, according to investigator assessment; discontinuation refers to discontinuation from treatment. Results are reported as number of patients with TEAEs for each of the indicated categories. Analysis performed on the SAF analysis set.

End point type	Secondary
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End point timeframe:

168 days (up to Cycle 6 Day 28 in Part B).

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The treatment arms 'Givinostat DL0 (50 mg b.i.d.) (Part A)', 'Givinostat DL1 (100 mg b.i.d.) (Part A)', 'Givinostat DL1 expanded (100 mg b.i.d.) (Part A)' and 'Givinostat DL6 (100 mg + 50 mg) (Part A)' are not applicable for this end point as only Part B study results are being presented.

End point values	Givinostat at MTD (100 mg b.i.d.) (Part B)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: participants				
TEAE	35			

Drug-related TEAE	33			
TESAE	1			
Drug-related TESAE	1			
Death due to any cause	0			
Grade 3 TEAE	12			
Grade 3 drug-related TEAE	10			
Grade 4 TEAE	0			
Grade 4 drug-related TEAE	0			
Grade 5 TEAE	0			
Discontinuation due to TEAE	2			
Discontinuation due to drug-related TEAE	2			
Discontinuation due to TESAE	0			
Discontinuation due to drug-related TESAE	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Maximum Plasma Concentration (Cmax) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study

End point title	Assessment of Maximum Plasma Concentration (Cmax) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Cmax following administration of givinostat for 1 cycle in Part A. PK calculations were performed by standard non-compartmental analysis. Results are reported for Cycle 1 Day 1 and Cycle 1 Day 28..

Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part A on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 1 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3 ^[11]	6	3	
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=3, 5, 3)	60.2 (± 43.1)	54.3 (± 17.2)	82.5 (± 24.4)	
ITF2374 Cycle 1 Day 1 (n=0, 5, 3)	9999999 (± 9999999)	3.74 (± 4.09)	5.69 (± 2.87)	
ITF2375 Cycle 1 Day 1 (n=0, 5, 2)	9999999 (± 9999999)	68.6 (± 21.2)	101 (± 24.5)	
Givinostat Cycle 1 Day 28 (n=3, 4, 3)	22.4 (± 8.92)	73.3 (± 31.9)	290 (± 330)	

ITF2374 Cycle 1 Day 28 (n=0, 4, 3)	9999999 (± 9999999)	19.7 (± 7.24)	31.3 (± 4.95)	
ITF2375 Cycle 1 Day 28 (n=2, 4, 3)	110 (± 22.8)	259 (± 75.9)	376 (± 215)	

Notes:

[11] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Time to Maximum Plasma Concentration (Tmax) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study

End point title	Assessment of Time to Maximum Plasma Concentration (Tmax) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Tmax following administration of givinostat for 1 cycle in Part A. PK calculations were performed by standard non-compartmental analysis. Results are reported for Cycle 1 Day 1 and Cycle 1 Day 28. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part A on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 1 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3 ^[12]	6	3	
Units: nanograms per millilitre (ng/ml)				
median (full range (min-max))				
Givinostat Cycle 1 Day 1 (n=3, 5, 3)	2.00 (1.92 to 3.00)	2.00 (2.00 to 2.00)	3.00 (2.00 to 3.00)	
ITF2374 Cycle 1 Day 1 (n=0, 4, 3)	9999999 (9999999 to 9999999)	8.00 (8.00 to 8.00)	8.00 (3.00 to 8.00)	
ITF2375 Cycle 1 Day 1 (n=0, 5, 2)	9999999 (9999999 to 9999999)	3.00 (2.00 to 3.00)	2.50 (2.00 to 3.00)	
Givinostat Cycle 1 Day 28 (n=3, 4 3)	3.90 (3.83 to 4.00)	1.50 (1.00 to 3.98)	2.05 (1.05 to 4.00)	
ITF2374 Cycle 1 Day 28 (n=0, 4, 3)	9999999 (9999999 to 9999999)	8.00 (0.00 to 8.00)	2.00 (1.05 to 4.05)	
ITF2375 Cycle 1 Day 28 (n=2, 4, 3)	2.00 (2.00 to 2.00)	1.99 (1.00 to 3.98)	4.00 (0.00 to 4.05)	

Notes:

[12] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Time of the Last Detectable Concentration (Tlast) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study

End point title	Assessment of Time of the Last Detectable Concentration (Tlast) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Tlast following administration of givinostat for 1 cycle in Part A. PK calculations were performed by standard non-compartmental analysis. Results are reported for Cycle 1 Day 1 and Cycle 1 Day 28. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part A on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 1 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3 ^[13]	6	3	
Units: hours				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=3, 5, 3)	7.97 (± 0.0462)	8.00 (± 0.00)	8.00 (± 0.00)	
ITF2374 Cycle 1 Day 1 (n=0, 4, 3)	9999999 (± 9999999)	8.00 (± 0.00)	8.00 (± 0.00)	
ITF2375 Cycle 1 Day 1 (n=0, 5, 2)	9999999 (± 9999999)	8.00 (± 0.00)	8.00 (± 0.00)	
Givinostat Cycle 1 Day 28 (n=3, 4, 3)	8.05 (± 0.249)	7.00 (± 2.01)	8.02 (± 0.0252)	
ITF2374 Cycle 1 Day 28 (n=0, 4, 3)	9999999 (± 9999999)	7.00 (± 2.01)	8.02 (± 0.0252)	
ITF2375 Cycle 1 Day 28 (n=2, 4, 3)	3.00 (± 1.41)	7.00 (± 2.01)	6.70 (± 2.30)	

Notes:

[13] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Area Under Plasma Concentration Versus the Time Curve up to the Last Detectable Concentration (AUClast) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study

End point title	Assessment of Area Under Plasma Concentration Versus the Time Curve up to the Last Detectable Concentration (AUClast) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of AUClast following administration of givinostat for 1 cycle in Part A. PK calculations were performed by standard non-

compartmental analysis and AUClast was calculated using the linear trapezoidal rule. Results are reported for Cycle 1 Day 1 and Cycle 1 Day 28. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter).

End point type	Secondary
End point timeframe:	
Blood samples were collected in Part A on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 1 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.	

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3 ^[14]	6	3	
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=3, 5, 3)	208 (± 136)	238 (± 55.6)	429 (± 109)	
ITF2374 Cycle 1 Day 1 (n=0, 5, 3)	9999999 (± 9999999)	14.4 (± 19.0)	29.6 (± 9.64)	
ITF2375 Cycle 1 Day 1 (n=0, 5, 2)	9999999 (± 9999999)	416 (± 153)	611 (± 146)	
Givinostat Cycle 1 Day 28 (n=3, 4, 3)	132 (± 45.1)	359 (± 203)	1100 (± 1050)	
ITF2374 Cycle 1 Day 28 (n=0, 4, 3)	9999999 (± 9999999)	102 (± 11.7)	158 (± 42.6)	
ITF2375 Cycle 1 Day 28 (n=2, 4, 3)	263 (± 192)	1390 (± 675)	1780 (± 1190)	

Notes:

[14] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Area Under Plasma Concentration Versus the Time Curve in the Dosing Interval (0-12 Hours) (AUC0-12) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study

End point title	Assessment of Area Under Plasma Concentration Versus the Time Curve in the Dosing Interval (0-12 Hours) (AUC0-12) of Givinostat and Metabolites (ITF2374 and ITF2375) in Part A of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of AUC0-12 following administration of givinostat for 1 cycle in Part A. PK calculations were performed by standard non-compartmental analysis and AUC0-12 was calculated using the linear trapezoidal rule. Results are reported for Cycle 1 Day 1 and Cycle 1 Day 28. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter).

End point type	Secondary
End point timeframe:	
Blood samples were collected in Part A on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 1 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.	

End point values	Givinostat DL0 (50 mg b.i.d.) (Part A PK analysis set)	Givinostat DL1 (100 mg b.i.d.) (Part A PK analysis set)	Givinostat DL6 (100 mg + 50 mg) (Part A PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3 ^[15]	6 ^[16]	3 ^[17]	
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=3, 5, 3)	235 (± 146)	289 (± 68.9)	508 (± 107)	
ITF2374 Cycle 1 Day 1 (n=0, 0, 0)	9999999 (± 9999999)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 1 Day 1 (n=0, 5, 2)	9999999 (± 9999999)	598 (± 259)	870 (± 182)	
Givinostat Cycle 1 Day 28 (n=3, 3, 3)	161 (± 51.8)	533 (± 223)	1180 (± 1050)	
ITF2374 Cycle 1 Day 28 (n=0, 0, 0)	9999999 (± 9999999)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 1 Day 28 (n=1, 3, 3)	863 (± 9999999)	2020 (± 1000)	2340 (± 970)	

Notes:

[15] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[16] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[17] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Cmax of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study

End point title	Assessment of Cmax of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Cmax following administration of givinostat for 2 cycles in Part B. PK calculations were performed by standard non-compartmental analysis. Following definition of the MTD in Part A, during Part B Cycle 1, givinostat was administered at 100 mg b.i.d. and during Part B Cycle 2 was administered at 100 mg, 75 mg and 50 mg b.i.d. (since dose reductions due to TEAEs were allowed from Cycle 2 onwards, as per protocol). Results are reported for Cycle 1 Day 1 and Cycle 2 Day 28 for the doses administered during Part B. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter). PK evaluation of givinostat 75 mg and 50 mg b.i.d. dose groups for Cycle 1 Day 1 not applicable (since all received 100 mg b.i.d.).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part B on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 2 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat 100 mg b.i.d. (Part B PK analysis set)	Givinostat 75 mg b.i.d. (Part B PK analysis set)	Givinostat 50 mg b.i.d. (Part B PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	12 ^[18]	2 ^[19]	
Units: ng/mL				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=34, 0, 0)	71.5 (± 34.4)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2374 Cycle 1 Day 1 (n=34, 0, 0)	7.85 (± 4.89)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 1 Day 1 (n=29, 0, 0)	161 (± 72.9)	9999999 (± 9999999)	9999999 (± 9999999)	
Givinostat Cycle 2 Day 28 (n=17, 12, 2)	90.8 (± 33.5)	64.0 (± 22.6)	62.6 (± 21.8)	
ITF2374 Cycle 2 Day 28 (n=17, 12, 2)	32.3 (± 21.0)	22.6 (± 11.2)	21.4 (± 0.424)	
ITF2375 Cycle 2 Day 28 (n=16, 9, 0)	320 (± 238)	203 (± 78.7)	9999999 (± 9999999)	

Notes:

[18] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[19] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Tmax of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study

End point title	Assessment of Tmax of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Tmax following administration of givinostat for 2 cycles in Part B. PK calculations were performed by standard non-compartmental analysis. Following definition of the MTD in Part A, during Part B Cycle 1, givinostat was administered at 100 mg b.i.d. and during Part B Cycle 2 was administered at 100 mg, 75 mg and 50 mg b.i.d. (since dose reductions due to TEAEs were allowed from Cycle 2 onwards, as per protocol). Results are reported for Cycle 1 Day 1 and Cycle 2 Day 28 for the doses administered during Part B. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter). PK evaluation of givinostat 75 mg and 50 mg b.i.d. dose groups for Cycle 1 Day 1 not applicable (since all received 100 mg b.i.d.).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part B on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 2 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat 100 mg b.i.d. (Part B PK analysis set)	Givinostat 75 mg b.i.d. (Part B PK analysis set)	Givinostat 50 mg b.i.d. (Part B PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	12 ^[20]	2 ^[21]	
Units: ng/mL				
median (full range (min-max))				
Givinostat Cycle 1 Day 1 (n=34, 0, 0)	2.00 (0.00 to 8.00)	9999999 (9999999 to 9999999)	9999999 (9999999 to 9999999)	

ITF2374 Cycle 1 Day 1 (n=34, 0, 0)	8.00 (2.08 to 8.17)	9999999 (9999999 to 9999999)	9999999 (9999999 to 9999999)	
ITF2375 Cycle 1 Day 1 (n=29, 0, 0)	3.00 (1.83 to 8.00)	9999999 (9999999 to 9999999)	9999999 (9999999 to 9999999)	
Givinostat Cycle 2 Day 28 (n=17, 12, 2)	2.00 (0.00 to 4.07)	2.00 (1.00 to 8.00)	0.985 (0.00 to 1.97)	
ITF2374 Cycle 2 Day 28 (n=17, 12, 2)	4.00 (0.00 to 8.00)	3.04 (1.00 to 8.00)	5.99 (3.97 to 8.00)	
ITF2375 Cycle 2 Day 28 (n=16, 9, 0)	2.00 (0.00 to 4.00)	2.00 (1.00 to 8.00)	9999999 (9999999 to 9999999)	

Notes:

[20] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[21] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Tlast of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study

End point title	Assessment of Tlast of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of Tlast following administration of givinostat for 2 cycles in Part B. PK calculations were performed by standard non-compartmental analysis. Following definition of the MTD in Part A, during Part B Cycle 1, givinostat was administered at 100 mg b.i.d. and during Part B Cycle 2 was administered at 100 mg, 75 mg and 50 mg b.i.d. (since dose reductions due to TEAEs were allowed from Cycle 2 onwards, as per protocol). Results are reported for Cycle 1 Day 1 and Cycle 2 Day 28 for the doses administered during Part B. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter). PK evaluation of givinostat 75 mg and 50 mg b.i.d. dose groups for Cycle 1 Day 1 not applicable (since all received 100 mg b.i.d.).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part B on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 2 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat 100 mg b.i.d. (Part B PK analysis set)	Givinostat 75 mg b.i.d. (Part B PK analysis set)	Givinostat 50 mg b.i.d. (Part B PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	12 ^[22]	2 ^[23]	
Units: hours				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=34, 0, 0)	7.42 (± 1.61)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2374 Cycle 1 Day 1 (n=34, 0, 0)	7.42 (± 1.61)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 1 Day 1 (n=29, 0, 0)	8.00 (± 0.0505)	9999999 (± 9999999)	9999999 (± 9999999)	
Givinostat Cycle 2 Day 28 (n=17, 12, 2)	8.00 (± 0.0340)	7.98 (± 0.0753)	7.99 (± 0.0212)	

ITF2374 Cycle 2 Day 28 (n=17, 12, 2)	8.00 (± 0.0340)	7.98 (± 0.0753)	7.99 (± 0.0212)	
ITF2375 Cycle 2 Day 28 (n=16, 9, 0)	7.75 (± 1.00)	8.00 (± 0.00)	9999999 (± 9999999)	

Notes:

[22] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[23] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of AUClast of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study

End point title	Assessment of AUClast of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of AUClast following administration of givinostat for 2 cycles in Part B. PK calculations were performed by standard non-compartmental analysis and AUClast was calculated using the linear trapezoidal rule. Following definition of the MTD in Part A, during Part B Cycle 1, givinostat was administered at 100 mg b.i.d. and during Part B Cycle 2 was administered at 100 mg, 75 mg and 50 mg b.i.d. (since dose reductions due to TEAEs were allowed from Cycle 2 onwards, as per protocol). Results are reported for Cycle 1 Day 1 and Cycle 2 Day 28 for the doses administered during Part B. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in the category title indicates number of patients analyzed for each parameter). PK evaluation of givinostat 75 mg and 50 mg b.i.d. dose groups for Cycle 1 Day 1 not applicable (since all received 100 mg b.i.d.).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part B on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 2 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat 100 mg b.i.d. (Part B PK analysis set)	Givinostat 75 mg b.i.d. (Part B PK analysis set)	Givinostat 50 mg b.i.d. (Part B PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	12 ^[24]	2 ^[25]	
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=34, 0, 0)	289 (± 130)	99999999 (± 99999999)	99999999 (± 99999999)	
ITF2374 Cycle 1 Day 1 (n=34, 0, 0)	28.5 (± 14.0)	99999999 (± 99999999)	99999999 (± 99999999)	
ITF2375 Cycle 1 Day 1 (n=29, 0, 0)	888 (± 439)	99999999 (± 99999999)	99999999 (± 99999999)	
Givinostat Cycle 2 Day 28 (n=17, 12, 2)	459 (± 145)	323 (± 107)	269 (± 78.5)	
ITF2374 Cycle 2 Day 28 (n=17, 12, 2)	216 (± 127)	161 (± 83.5)	145 (± 20.9)	
ITF2375 Cycle 2 Day 28 (n=16, 9, 0)	1830 (± 1660)	1210 (± 585)	99999999 (± 99999999)	

Notes:

[24] - 99999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[25] - 99999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

Secondary: Assessment of AUC0-12 of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study

End point title	Assessment of AUC0-12 of Givinostat and Metabolites (ITF2374 and ITF2375) in Part B of the Study
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End point description:

PK evaluation of givinostat and metabolites (ITF2374 and ITF2375) by assessment of AUC0-12 following administration of givinostat for 2 cycles in Part B. PK calculations were performed by standard non-compartmental analysis and AUClast was calculated using the linear trapezoidal rule. Following definition of the MTD in Part A, during Part B Cycle 1, givinostat was administered at 100 mg b.i.d. and during Part B Cycle 2 was administered at 100 mg, 75 mg and 50 mg b.i.d. (since dose reductions due to TEAEs were allowed from Cycle 2 onwards, as per protocol). Results are reported for Cycle 1 Day 1 and Cycle 2 Day 28 for the doses administered during Part B. Analysis performed on PK analysis set. Only patients with data available for analysis are presented (n in category title indicates number of patients analyzed for each parameter). PK evaluation of givinostat 75 mg and 50 mg b.i.d. dose groups for Cycle 1 Day 1 not applicable (since all received 100 mg b.i.d.).

End point type	Secondary
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End point timeframe:

Blood samples were collected in Part B on Cycle 1 Day 1: pre-dose and 2, 3 and 8 hours post-dose; and on Cycle 2 Day 28: pre-dose and 1, 2, 4 and 8 hours post-dose.

End point values	Givinostat 100 mg b.i.d. (Part B PK analysis set)	Givinostat 75 mg b.i.d. (Part B PK analysis set)	Givinostat 50 mg b.i.d. (Part B PK analysis set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34 ^[26]	12 ^[27]	2 ^[28]	
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Givinostat Cycle 1 Day 1 (n=29, 0, 0)	372 (± 137)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2374 Cycle 1 Day 1 (n=0, 0, 0)	9999999 (± 9999999)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 1 Day 1 (n=22, 0, 0)	1080 (± 619)	9999999 (± 9999999)	9999999 (± 9999999)	
Givinostat Cycle 2 Day 28 (n=17, 11, 2)	561 (± 176)	410 (± 129)	326 (± 54.0)	
ITF2374 Cycle 2 Day 28 (n=0, 0, 0)	9999999 (± 9999999)	9999999 (± 9999999)	9999999 (± 9999999)	
ITF2375 Cycle 2 Day 28 (n=14, 7, 0)	2460 (± 2450)	1460 (± 608)	9999999 (± 9999999)	

Notes:

[26] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[27] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

[28] - 9999999=not calculated. For certain parameters, concentration data not available for PK analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

168 days for Part A and 168 days for Part B (Cycle 1 through Cycle 6 for each phase of study; each cycle 28 days).

Adverse event reporting additional description:

TEAEs are reported for Part A and Part B and include events with an onset on or after the first administration of study drug until the end of study visit (or 7 days after the last drug intake for any patient permanently discontinuing study treatment).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Givinostat DL0 (50 mg b.i.d.) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL0 (50 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

Reporting group title	Givinostat DL1 (100 mg b.i.d.) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL1 (100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

Reporting group title	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
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Reporting group description:

Following initial assignment of 3 patients to DL1 in Part A, a further 3 patients were assigned to DL1 so this treatment group is referred to as "DL1 expanded" (patients received givinostat by oral administration at 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle).

Reporting group title	Givinostat DL6 (100 mg + 50 mg) (Part A)
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Reporting group description:

In Part A, 3 patients were assigned to receive givinostat by oral administration at DL 6 (100 mg in the morning and 50 mg in the evening, i.e. 12 hours after). Patients were treated for up to 6 cycles in (28 days in each cycle).

Reporting group title	Givinostat at MTD (100 mg b.i.d.) (Part B)
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Reporting group description:

In Part B, patients were assigned to receive the starting dose of givinostat by oral administration at the MTD determined in Part A (i.e. 100 mg b.i.d.). Patients were treated for up to 6 cycles (28 days in each cycle). Based on evaluations performed as part of the visit procedures on Day 28 of each cycle up to Cycle 5 and/or in any necessary additional study visit, the givinostat doses could be decreased for any patients that met dose reduction criteria.

Serious adverse events	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Thrombophlebitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Givinostat DL6 (100 mg + 50 mg) (Part A)	Givinostat at MTD (100 mg b.i.d.) (Part B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	
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: 5 %

Non-serious adverse events	Givinostat DL0 (50 mg b.i.d.) (Part A)	Givinostat DL1 (100 mg b.i.d.) (Part A)	Givinostat DL1 expanded (100 mg b.i.d.) (Part A)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Erythromelalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1

Chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Early satiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Irritability subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Investigations			
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Electrocardiogram qt prolonged subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Weight decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 2	1 / 3 (33.33%) 1
Head discomfort subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0

Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemolytic anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	0	2	4
Thrombocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	2	4	3
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	6	0
Faeces soft			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Acute kidney injury subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Chromaturia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Chondrocalcinosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Rheumatoid arthritis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations Localised infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Parainfluenzae virus infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Givinostat DL6 (100 mg + 50 mg) (Part A)	Givinostat at MTD (100 mg b.i.d.) (Part B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	35 / 35 (100.00%)	
Vascular disorders			
Erythromelalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Flushing			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	10 / 35 (28.57%)	
occurrences (all)	1	22	
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Early satiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	
occurrences (all)	1	3	
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	4	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	3	
Psychiatric disorders			

Confusional state subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Irritability subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	14 / 35 (40.00%) 21	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Electrocardiogram qt prolonged subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 35 (0.00%) 0	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 35 (8.57%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Dysgeusia subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	3 / 35 (8.57%) 3	

Head discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 35 (2.86%) 1	
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Memory impairment subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	6 / 35 (17.14%) 14	
Haemolytic anaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	16 / 35 (45.71%) 22	
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 3	8 / 35 (22.86%) 9	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	4 / 35 (11.43%) 5	
Constipation			

subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	20 / 35 (57.14%)	
occurrences (all)	5	39	
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 35 (14.29%)	
occurrences (all)	0	5	
Faeces soft			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	10 / 35 (28.57%)	
occurrences (all)	0	13	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 35 (11.43%)	
occurrences (all)	1	4	
Pruritus			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 35 (8.57%) 3	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Chromaturia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 35 (0.00%) 0	
Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 35 (0.00%) 0	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	
Chondrocalcinosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Rheumatoid arthritis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Infections and infestations Localised infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Parainfluenzae virus infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 35 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 35 (5.71%) 2	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	4	
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 35 (14.29%)	
occurrences (all)	0	6	
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2013	1.Inclusion criterion regarding contraception and contraceptive methods updated, as requested by French Regulatory Authority. 2.Patient numbering sections updated as per study electronic Case Report Form. 3.Exploratory endpoint of Part B added, in order to also evaluate preliminary efficacy of givinostat according to the revised ELN Response Criteria.
29 July 2015	1.Preclinical rationale wording amended. 2.Approved drugs for treatment of PV and Myelofibrosis updated. 3.Neuromuscular disorders added as an indication. 4.Necessity to receive all approvals before starting long-term study DSC/11/2357/44 clarified. 5.Contract Manufacturing Organization as possible delegate for management of the study drug added. 6.Exclusion criterion updated to clarify "any other investigational drug or device". 7.Instructions for study drug administration and dispensing were specified. 8.Spleen evaluations in Part B clarified. 9.Explanation that in case patient completes the study (i.e. performs all evaluations at Cycle 6 Day 28), these evaluations also counted for end of study visit. 10.Specification that in case patient completes the study (i.e. performs all evaluations requested at Cycle 6 Day 28) and is eligible to continue study drug treatment in DSC/11/2357/44, these evaluations could also count for the pre-treatment evaluations of DSC/11/2357/44. 11.Population for all efficacy analyses was clarified. 12.The SAE Form, AEs definition and details of Sponsor's Drug Safety Unit were updated in the safety section. 13.Sections related to Part B were updated based on definition of the MTD of givinostat as chronic treatment in PV patients (relating to tolerability data for patients enrolled in Part A). 14.Dose modification rules to be applied in Part B (and in Part A) were updated. 15.75 mg strength added. 16.Pharmacodynamic evaluations added. 17.Calculation of estimated Glomerular Filtration Rate clarified, as agreed with German Regulatory Authority. 18.Evaluation of Urea updated. 19.Performing additional electrocardiogram evaluations (if first evaluation demonstrates a prolonged QTc interval) was clarified. 20.In Part B, recommendation that patients should arrive after an overnight fast at all study visits requiring a blood test was clarified. 21.Collection of blood sample for mutational status analysis during Part B added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations or caveats are applicable to this summary of the results.

Notes: