Clinical trial results:
A Phase Ib/IIb, open-label, multi-center study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2009-010548-32
Trial protocol	DE SE AT ES BE GB HU IT
Global end of trial date	29 April 2019

Results information

Result version number	v1 (current)
This version publication date	15 May 2020
First version publication date	15 May 2020

Trial information

Trial identification

Sponsor protocol code	CLBH589H2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00946647
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase: To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RPIID) of oral PAN in combination with a fixed dose of 5-Aza in adult patients with International Prognostic Scoring System intermediate 2 (IPSS INT-2) or high risk MDS, CMML, or AML.

Phase ll: To assess preliminary efficacy of treatment with the panobinostat and 5-Aza combination at the RPIID relative to treatment with single agent 5-Aza through the assessment of composite CR (CR or CRi or bone marrow CR).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 2009
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	Austria: 4
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 4

Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	113
EEA total number of subjects	65

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)	29
From 65 to 84 years	83
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

In phase l a total of 31 patients were treated with escalating dose of PAN,20 mg 30 mg & 40 mg.
In phase ll a total of 82 patients were actually randomized with 40 patients assigned to PAN+5-Aza & 42 patients to 5-Aza.
Treatment was assigned sequentially for the phase Ib. Randomization applies only for the phase IIb part.

Pre-assignment

Screening details:

For phase I, approximately 26 patients were planned to be enrolled in cohorts of at least three MTD evaluable patients per dose level.
For phase ll, approximately 80 patients were planned to be enrolled, 40 patients per arm.

Period 1

Period 1 title	Phase l part
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	PAN + 5-Aza 20 mg

Arm description:

In this escalating phase, participants took panobinostat of 20 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.

Arm type	Experimental
Investigational medicinal product name	5-Azacytidine (5-Aza)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose of 5-Aza was 75 mg/m2. 5-Aza was to be administered subcutaneously daily for seven days.

Investigational medicinal product name	oral panobinostat
Investigational medicinal product code	LBH589
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dose of 20 mg delivered once daily on Day 3, 5, 8, 10, 12, and 15, in combination with 5-Aza. Immediate-release hard gelatin capsules in strengths of 5 mg, 10 mg (when available) and 20 mg which were given on a flat scale of mg per given day.

Arm title	PAN + 5-Aza 30 mg

Arm description:

In this escalating phase, participants took panobinostat of 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.

Arm type	Experimental

Investigational medicinal product name	5-Azacytidine (5-Aza)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose of 5-Aza was 75 mg/m2. 5-Aza was to be administered subcutaneously daily for seven days.

Investigational medicinal product name	oral panobinostat
Investigational medicinal product code	LBH589
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dose of 30 mg starting with 20 mg delivered once daily on
Day 3, 5, 8, 10, 12, and 15 in combination with 5-Aza. Immediate-release hard gelatin capsules in strengths of 5 mg, 10 mg (when available) and 20 mg which were given on a flat scale of mg per given day.

Arm title	PAN + 5-Aza 40 mg

Arm description:

In this escalating phase, participants took panobinostat of 40 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle

Arm type	Experimental
Investigational medicinal product name	oral panobinostat
Investigational medicinal product code	LBH589
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dose of 40 mg delivered once daily. immediate-release hard gelatin capsules in strengths of 5 mg, 10 mg (when available) and 20 mg which were given on a flat scale of mg per given day.

Investigational medicinal product name	5-Azacytidine (5-Aza)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose of 5-Aza was 75 mg/m2. 5-Aza was to be administered subcutaneously daily for seven days.

Number of subjects in period 1[1]	PAN + 5-Aza 20 mg	PAN + 5-Aza 30 mg	PAN + 5-Aza 40 mg
Started	6	18	7
Completed	0	0	0
Not completed	6	18	7
Consent withdrawn by subject	1	4	3
Disease progression	3	6	1
Adverse event, non-fatal	2	5	3
Abnormal values	-	2	-

Reason missing	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects in the dose escalation phase (part 1/phase l) were fewer than those in the dose escalation phase (part 2/phase ll)

Period 2

Period 2 title	Phase ll part
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Panobinostat + 5-Azacytidine

Arm description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Arm type	Experimental
Investigational medicinal product name	5-Azacytidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose of 5-Aza was 75 mg/m2. 5-Aza was to be administered subcutaneously daily for seven days.

Investigational medicinal product name	Oral panobinostat
Investigational medicinal product code	LBH589
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

30 mg of oral panobinostat once daily on Day 3, 5, 8, 10, 12, and 15 in combination with 5-Aza.

Arm title	5-Azacytidine

Arm description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis. Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Arm type	Active comparator
Investigational medicinal product name	5-Azacytidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose of 5-Aza was 75 mg/m2. 5-Aza was to be administered subcutaneously daily for seven days.

Number of subjects in period 2	Panobinostat + 5-Azacytidine	5-Azacytidine
Started	40	42
Completed	0	0
Not completed	40	42
Adverse event, serious fatal	7	4
Consent withdrawn by subject	8	6
Disease progression	6	14
Subj cond no longer required study drug	2	-
Adverse event, non-fatal	10	6
Administrative problems	3	8
Untreated	-	2
Protocol deviation	4	2

Baseline characteristics

Reporting groups	
Reporting group title	PAN + 5-Aza 20 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 20 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Reporting group title	PAN + 5-Aza 30 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Reporting group title	PAN + 5-Aza 40 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 40 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle	

Reporting group values	PAN + 5-Aza 20 mg	PAN + 5-Aza 30 mg	PAN + 5-Aza 40 mg
Number of subjects	6	18	7
Age Categorical Units: participants			
< 65	1	5	1
>= 65	5	13	6
Sex: Female, Male Units: participants			
Female	2	10	4
Male	4	8	3
Race/Ethnicity, Customized Units: Subjects			
Caucasian	5	15	6
Black	0	0	1
Asian	0	0	0
Other	1	3	0

Reporting group values	Total		
Number of subjects	31		
Age Categorical Units: participants			
< 65	7		
>= 65	24		
Sex: Female, Male Units: participants			
Female	16		
Male	15		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	26		
Black	1		

Asian	0		
Other	4		

Subject analysis sets

Subject analysis set title	PAN + 5-Aza 20 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In this escalating phase, participants took panobinostat of 20 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.

Subject analysis set title	PAN + 5-Aza 30 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In this escalating phase, participants took panobinostat of 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.

Subject analysis set title	Panobinostat + 5-Azacytidine (MDS-CMML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Subject analysis set title	5-Azacytidine (MDS-CMML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Subject analysis set title	Panobinostat + 5-Azacytidine (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Subject analysis set title	5-Azacytidine (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Subject analysis set title	Panobinostat + 5-Azacytidine (AML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Subject analysis set title	5-Azacytidine (AML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Reporting group values	PAN + 5-Aza 20 mg	PAN + 5-Aza 30 mg	Panobinostat + 5-Azacytidine (MDS-CMML)
Number of subjects	5	14	31
Age Categorical Units: participants			
< 65	0	0	0
>= 65	0	0	0
Sex: Female, Male Units: participants			
Female	0	0	0
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Black			
Asian			
Other			

Reporting group values	5-Azacytidine (MDS-CMML)	Panobinostat + 5-Azacytidine (FAS)	5-Azacytidine (FAS)
Number of subjects	29	40	42
Age Categorical Units: participants			
< 65	0	14	8
>= 65	0	26	34
Sex: Female, Male Units: participants			
Female	0	11	17
Male	0	29	25
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Black			
Asian			
Other			

Reporting group values	Panobinostat + 5-Azacytidine (AML)	5-Azacytidine (AML)	
Number of subjects	9	13	
Age Categorical Units: participants			
< 65			
>= 65			
Sex: Female, Male Units: participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Black			

Asian Other			

End points

End points reporting groups

Reporting group title	PAN + 5-Aza 20 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 20 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Reporting group title	PAN + 5-Aza 30 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Reporting group title	PAN + 5-Aza 40 mg
Reporting group description:	
In this escalating phase, participants took panobinostat of 40 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle	
Reporting group title	Panobinostat + 5-Azacytidine
Reporting group description:	
In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.	
Reporting group title	5-Azacytidine
Reporting group description:	
The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis. Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.	
Subject analysis set title	PAN + 5-Aza 20 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In this escalating phase, participants took panobinostat of 20 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Subject analysis set title	PAN + 5-Aza 30 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In this escalating phase, participants took panobinostat of 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15 and a fixed dose of 5-Azacytidine (5-Aza) at 75 mg/m2/day for 7 days in Week 1 of each cycle.	
Subject analysis set title	Panobinostat + 5-Azacytidine (MDS-CMML)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.	
Subject analysis set title	5-Azacytidine (MDS-CMML)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis. Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.	
Subject analysis set title	Panobinostat + 5-Azacytidine (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Subject analysis set title	5-Azacytidine (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Subject analysis set title	Panobinostat + 5-Azacytidine (AML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Subject analysis set title	5-Azacytidine (AML)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day 7.

Primary: Incidence of dose limiting toxicity (DLT) (Phase I)

End point title	Incidence of dose limiting toxicity (DLT) (Phase I)[1]

End point description:

Dose limiting toxicity (DLT) was defined as a toxicity requiring treatment withdrawal and included the following: Non-hematologic toxicity qualifying for DLT and Hematologic toxicity qualifying for DLT

End point type	Primary

End point timeframe:

within the first 28 days (cycle 1)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was planned for this endpoint

End point values	PAN + 5-Aza 20 mg	PAN + 5-Aza 30 mg	PAN + 5-Aza 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	14	7	
Units: Participants				
Number of participants with DLTs	1	3	2	
Number of DLTs	2	6	4	

Statistical analyses

No statistical analyses for this end point

Primary: Composite Complete Response(Phase IIb)

End point title	Composite Complete Response(Phase IIb)[2]

End point description:

Composite complete response is defined as complete response (CR), Complete response with incomplete blood count recovery (CRi) or bone marrow complete response (BM-CR).

End point type	Primary

End point timeframe:

40 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical analysis was planned for this endpoint

End point values	Panobinostat + 5-Azacytidine	5-Azacytidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: Percentage of participants				
number (confidence interval 95%)	27.5 (14.60 to 43.89)	14.3 (5.43 to 28.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response other than Composite clinical response for myeloid dysplastic syndromes(MDS)/chronic myelomonocytic leukemia (CMML) patients per Investigator (Phase llb)

End point title	Clinical response other than Composite clinical response for myeloid dysplastic syndromes(MDS)/chronic myelomonocytic leukemia (CMML) patients per Investigator (Phase llb)

End point description:

This is the best overall response as measured by Clinical response. Clinical response is defined as having complete remission (CR), bone marrow complete remission (BM-CR), partial remission or hematologic improvement (HI).

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine (MDS-CMML)	5-Azacytidine (MDS-CMML)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: Percentage of subjects				
number (confidence interval 95%)	41.9 (24.5 to 60.9)	41.4 (23.5 to 61.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response other than Composite clinical response for Acute myelogenous leukemia (AML) patients per Investigator (Phase IIb)

End point title	Clinical response other than Composite clinical response for Acute myelogenous leukemia (AML) patients per Investigator (Phase IIb)

End point description:

This is the best overall response as measured by Clinical response. Clinical response is defined as having complete remission (CR), complete remission with incomplete blood count recovery (CRi) or partial remission.

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine (AML)	5-Azacytidine (AML)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	13		
Units: Percentage of participants				
number (confidence interval 95%)	22.2 (2.8 to 60.0)	30.8 (9.1 to 61.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) assessed by Best overall response: Participants with MDS/CMML per Investigator (phase IIb)

End point title	Overall response rate (ORR) assessed by Best overall response: Participants with MDS/CMML per Investigator (phase IIb)

End point description:

Best overall response as measured by complete remission (CR) or bone marrow CR (BM-CR) or partial remission (PR) or hematologic improvement (HI).

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine (MDS-CMML)	5-Azacytidine (MDS-CMML)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: Percentage of participants				
number (not applicable)				

Clinical response (CR, BM-CR, PR, HI)	41.9	41.4		
Complete remission (CR)	16.1	6.9		
Bone marrow CR (BM-CR)	12.9	3.4		
Partial remission (PR)	0.0	6.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)assessed by Best overall response: Participants with AML per Investigator (phase llb)

End point title	Overall response rate (ORR)assessed by Best overall response: Participants with AML per Investigator (phase llb)

End point description:

Best overall response as measured by complete remission (CR) or complete response with incomplete blood count recovery (CRi)or partial remission (PR).

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine (AML)	5-Azacytidine (AML)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	13		
Units: Percentage of participants				
number (not applicable)				
Clinical response (CR, CRi, PR)	22.2	30.8		
Complete remission (CR)	11.1	15.4		
Compl remiss. with incompl blood cnt	11.1	7.7		
Partial remission (PR)	0.0	7.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic Improvement (HI) for myeloid dysplastic syndromes(MDS)/chronic myelomonocytic leukemia (CMML) patients per

End point title	Hematologic Improvement (HI) for myeloid dysplastic syndromes(MDS)/chronic myelomonocytic leukemia (CMML) patients per Investigator (Phase llb)

End point description:

Hematologic response consists of Erythroid response (HI-E), Platelet response (HI-P) and Neutrophil response (HI-N).
HI-E: Hgb increase by ≥ 1.5 g/dL over pretreatment & relevant reduction of units of RBC transfusions by an absolute number of at least 4 units of PRBCs/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will

count in the RBC transfusion response evaluation.
HI-P: Absolute increase of ≥ 30 x 109/L over pretreatment or patients starting with ≥ 20 x 109/L platelets OR increase from <20 x 109/L at pretreatment to > 20 x 109/L and by at least 100%.
HI-N: At least 100% increase and an absolute increase > 0.5 x 109/L over pretreatment value.

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine (MDS-CMML)	5-Azacytidine (MDS-CMML)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: Percentage of participants				
number (confidence interval 95%)				
Erythroid response (HI-E)	25.8 (11.9 to 44.6)	31.0 (15.3 to 50.8)		
Platelet response (HI-P)	35.5 (19.2 to 54.6)	24.1 (10.3 to 43.5)		
Neutrophil response (HI-N)	19.4 (7.5 to 37.5)	13.8 (3.9 to 31.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year survival rate (Phase IIb)

End point title	1-year survival rate (Phase IIb)

End point description:

Overall survival was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last contact. Patients not known to have died were censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date was longer than 3 months and 2 weeks (104 days) during the first year after study evaluation completion, and longer than 6 months and 2 weeks (194 days), thereafter. The 1-year survival rate was obtained from the Kaplan-Meier analysis of overall survival, and its variance was estimated by Greenwood's formula.

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine	5-Azacytidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: months				
median (confidence interval 95%)	14.9 (10.4 to 999)	15.6 (11.4 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) (Phase IIb)

End point title	Time to progression (TTP) (Phase IIb)

End point description:

Time to progression (TTP) was defined as the time from the date of randomization to the date of the first documented PD per investigator's assessment or death due to study indication.
Time to progression was analyzed by the Kaplan Meier method. Based on the Guidelines for Implementation of international working group (IWG) response criteria in AML, MDS and CMML according to Cheson 2003 and 2006.

End point type	Secondary

End point timeframe:

40 weeks

End point values	Panobinostat + 5-Azacytidine	5-Azacytidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: months				
median (confidence interval 95%)	99 (11.1 to 999)	15.2 (11.0 to 999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	PAN + 5-Aza

Reporting group description:

In phase II: Panobinostat : Rapid Phase II doses at 30 mg delivered orally at Day 3, Day 5, Day 8, Day 10, Day 12, Day 15. In both phases, dose of 5-Azacytidine was 75 mg/m^2, subcutaneously Daily for Day 1 to Day 7.

Reporting group title	All Patients

Reporting group description:

Patients in the Panobinostat + 5-Azacytidine arm and in the 5-Azacytidine arm.

Reporting group title	5-Aza

Reporting group description:

The dose of 5-Aza was fixed at 75 mg/m2/day for 7 days in Week 1 of each cycle. 5-Aza was sourced locally, except in 4 countries (Hungary, Switzerland, UK, and Spain, for which a central purchase was used by Novartis.
Dose of 5-Azacytidine : 75 mg/m^2 subcutaneously daily from Day 1 to Day

Serious adverse events	PAN + 5-Aza	All Patients	5-Aza
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 38 (73.68%)	56 / 80 (70.00%)	28 / 42 (66.67%)
number of deaths (all causes)	6	9	3
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign anorectal neoplasm			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large cell lung cancer metastatic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meningioma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 38 (7.89%)	3 / 80 (3.75%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 38 (0.00%)	2 / 80 (2.50%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 38 (2.63%)	2 / 80 (2.50%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			

subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transfusion reaction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 38 (0.00%)	2 / 80 (2.50%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	10 / 38 (26.32%)	16 / 80 (20.00%)	6 / 42 (14.29%)
occurrences causally related to treatment / all	8 / 17	9 / 24	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	1 / 38 (2.63%)	2 / 80 (2.50%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 38 (7.89%)	6 / 80 (7.50%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	2 / 3	3 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	2 / 80 (2.50%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 38 (2.63%)	2 / 80 (2.50%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 38 (0.00%)	2 / 80 (2.50%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue haematoma			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pollakiuria			

subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacterial sepsis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	3 / 80 (3.75%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			

subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lower respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 38 (0.00%)	3 / 80 (3.75%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 0	1 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral bacterial infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal abscess			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	8 / 38 (21.05%)	12 / 80 (15.00%)	4 / 42 (9.52%)
occurrences causally related to treatment / all	4 / 9	5 / 13	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 38 (10.53%)	8 / 80 (10.00%)	4 / 42 (9.52%)
occurrences causally related to treatment / all	2 / 5	2 / 9	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Septic shock			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Tooth infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 38 (2.63%)	1 / 80 (1.25%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 38 (0.00%)	1 / 80 (1.25%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PAN + 5-Aza	All Patients	5-Aza
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	76 / 80 (95.00%)	38 / 42 (90.48%)
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 38 (5.26%)	7 / 80 (8.75%)	5 / 42 (11.90%)
occurrences (all)	2	9	7
Hypotension			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	3	5	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 38 (26.32%)	16 / 80 (20.00%)	6 / 42 (14.29%)
occurrences (all)	12	24	12
Chills			
subjects affected / exposed	3 / 38 (7.89%)	6 / 80 (7.50%)	3 / 42 (7.14%)
occurrences (all)	4	7	3
Fatigue			
subjects affected / exposed	10 / 38 (26.32%)	26 / 80 (32.50%)	16 / 42 (38.10%)
occurrences (all)	25	44	19
Injection site erythema			
subjects affected / exposed	3 / 38 (7.89%)	6 / 80 (7.50%)	3 / 42 (7.14%)
occurrences (all)	4	10	6
Injection site rash			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	4	2
Injection site pain			
subjects affected / exposed	2 / 38 (5.26%)	5 / 80 (6.25%)	3 / 42 (7.14%)
occurrences (all)	2	5	3
Malaise			

subjects affected / exposed	1 / 38 (2.63%)	5 / 80 (6.25%)	4 / 42 (9.52%)
occurrences (all)	1	6	5
Injection site reaction			
subjects affected / exposed	3 / 38 (7.89%)	5 / 80 (6.25%)	2 / 42 (4.76%)
occurrences (all)	23	26	3
Non-cardiac chest pain			
subjects affected / exposed	4 / 38 (10.53%)	6 / 80 (7.50%)	2 / 42 (4.76%)
occurrences (all)	5	7	2
Oedema peripheral			
subjects affected / exposed	8 / 38 (21.05%)	17 / 80 (21.25%)	9 / 42 (21.43%)
occurrences (all)	10	20	10
Pain			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	3	4	1
Pyrexia			
subjects affected / exposed	18 / 38 (47.37%)	27 / 80 (33.75%)	9 / 42 (21.43%)
occurrences (all)	26	47	21
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 38 (18.42%)	13 / 80 (16.25%)	6 / 42 (14.29%)
occurrences (all)	9	17	8
Dyspnoea			
subjects affected / exposed	2 / 38 (5.26%)	6 / 80 (7.50%)	4 / 42 (9.52%)
occurrences (all)	2	7	5
Epistaxis			
subjects affected / exposed	5 / 38 (13.16%)	11 / 80 (13.75%)	6 / 42 (14.29%)
occurrences (all)	7	13	6
Oropharyngeal pain			
subjects affected / exposed	0 / 38 (0.00%)	5 / 80 (6.25%)	5 / 42 (11.90%)
occurrences (all)	0	7	7
Productive cough			

subjects affected / exposed	0 / 38 (0.00%)	3 / 80 (3.75%)	3 / 42 (7.14%)
occurrences (all)	0	3	3
Rhinorrhoea			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Insomnia			
subjects affected / exposed	5 / 38 (13.16%)	8 / 80 (10.00%)	3 / 42 (7.14%)
occurrences (all)	9	12	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	5 / 80 (6.25%)	2 / 42 (4.76%)
occurrences (all)	7	10	3
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 38 (10.53%)	5 / 80 (6.25%)	1 / 42 (2.38%)
occurrences (all)	8	10	2
Blood albumin decreased			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
C-reactive protein increased			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 38 (7.89%)	3 / 80 (3.75%)	0 / 42 (0.00%)
occurrences (all)	3	3	0
Blood creatinine increased			
subjects affected / exposed	4 / 38 (10.53%)	4 / 80 (5.00%)	0 / 42 (0.00%)
occurrences (all)	5	5	0
Haemoglobin decreased			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	6	7	1
Neutrophil count decreased			

subjects affected / exposed	6 / 38 (15.79%)	9 / 80 (11.25%)	3 / 42 (7.14%)
occurrences (all)	31	34	3
Platelet count decreased			
subjects affected / exposed	8 / 38 (21.05%)	10 / 80 (12.50%)	2 / 42 (4.76%)
occurrences (all)	36	38	2
Weight decreased			
subjects affected / exposed	7 / 38 (18.42%)	13 / 80 (16.25%)	6 / 42 (14.29%)
occurrences (all)	8	15	7
White blood cell count decreased			
subjects affected / exposed	4 / 38 (10.53%)	4 / 80 (5.00%)	0 / 42 (0.00%)
occurrences (all)	4	4	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 38 (7.89%)	5 / 80 (6.25%)	2 / 42 (4.76%)
occurrences (all)	3	5	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 38 (7.89%)	4 / 80 (5.00%)	1 / 42 (2.38%)
occurrences (all)	3	4	1
Sinus tachycardia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 38 (13.16%)	8 / 80 (10.00%)	3 / 42 (7.14%)
occurrences (all)	7	10	3
Dysgeusia			
subjects affected / exposed	3 / 38 (7.89%)	5 / 80 (6.25%)	2 / 42 (4.76%)
occurrences (all)	3	5	2
Headache			
subjects affected / exposed	7 / 38 (18.42%)	14 / 80 (17.50%)	7 / 42 (16.67%)
occurrences (all)	14	22	8
Syncope			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	2	4	2
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	12 / 38 (31.58%)	26 / 80 (32.50%)	14 / 42 (33.33%)
occurrences (all)	39	55	16
Febrile neutropenia			
subjects affected / exposed	6 / 38 (15.79%)	8 / 80 (10.00%)	2 / 42 (4.76%)
occurrences (all)	6	8	2
Leukopenia			
subjects affected / exposed	4 / 38 (10.53%)	5 / 80 (6.25%)	1 / 42 (2.38%)
occurrences (all)	8	9	1
Lymphopenia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Neutropenia			
subjects affected / exposed	16 / 38 (42.11%)	26 / 80 (32.50%)	10 / 42 (23.81%)
occurrences (all)	40	72	32
Pancytopenia			
subjects affected / exposed	3 / 38 (7.89%)	4 / 80 (5.00%)	1 / 42 (2.38%)
occurrences (all)	4	5	1
Thrombocytopenia			
subjects affected / exposed	18 / 38 (47.37%)	28 / 80 (35.00%)	10 / 42 (23.81%)
occurrences (all)	86	110	24
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 38 (15.79%)	8 / 80 (10.00%)	2 / 42 (4.76%)
occurrences (all)	6	9	3
Abdominal pain upper			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	2	4	2
Constipation			
subjects affected / exposed	10 / 38 (26.32%)	26 / 80 (32.50%)	16 / 42 (38.10%)
occurrences (all)	26	51	25
Diarrhoea			
subjects affected / exposed	22 / 38 (57.89%)	31 / 80 (38.75%)	9 / 42 (21.43%)
occurrences (all)	41	56	15
Dry mouth			

subjects affected / exposed	3 / 38 (7.89%)	3 / 80 (3.75%)	0 / 42 (0.00%)
occurrences (all)	3	3	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	3	4	1
Haemorrhoids			
subjects affected / exposed	5 / 38 (13.16%)	6 / 80 (7.50%)	1 / 42 (2.38%)
occurrences (all)	5	6	1
Nausea			
subjects affected / exposed	23 / 38 (60.53%)	41 / 80 (51.25%)	18 / 42 (42.86%)
occurrences (all)	57	97	40
Stomatitis			
subjects affected / exposed	2 / 38 (5.26%)	6 / 80 (7.50%)	4 / 42 (9.52%)
occurrences (all)	2	17	15
Toothache			
subjects affected / exposed	1 / 38 (2.63%)	4 / 80 (5.00%)	3 / 42 (7.14%)
occurrences (all)	1	4	3
Vomiting			
subjects affected / exposed	16 / 38 (42.11%)	28 / 80 (35.00%)	12 / 42 (28.57%)
occurrences (all)	29	46	17
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Ecchymosis			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	4	5	1
Erythema			
subjects affected / exposed	1 / 38 (2.63%)	5 / 80 (6.25%)	4 / 42 (9.52%)
occurrences (all)	1	5	4
Pain of skin			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Petechiae			
subjects affected / exposed	3 / 38 (7.89%)	4 / 80 (5.00%)	1 / 42 (2.38%)
occurrences (all)	4	5	1

Pruritus			
subjects affected / exposed	4 / 38 (10.53%)	7 / 80 (8.75%)	3 / 42 (7.14%)
occurrences (all)	4	7	3
Rash			
subjects affected / exposed	6 / 38 (15.79%)	10 / 80 (12.50%)	4 / 42 (9.52%)
occurrences (all)	7	11	4
Rash maculo-papular			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Urticaria			
subjects affected / exposed	4 / 38 (10.53%)	4 / 80 (5.00%)	0 / 42 (0.00%)
occurrences (all)	5	5	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	4	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 38 (7.89%)	7 / 80 (8.75%)	4 / 42 (9.52%)
occurrences (all)	4	10	6
Back pain			
subjects affected / exposed	5 / 38 (13.16%)	9 / 80 (11.25%)	4 / 42 (9.52%)
occurrences (all)	9	14	5
Myalgia			
subjects affected / exposed	3 / 38 (7.89%)	5 / 80 (6.25%)	2 / 42 (4.76%)
occurrences (all)	3	8	5
Musculoskeletal pain			
subjects affected / exposed	2 / 38 (5.26%)	5 / 80 (6.25%)	3 / 42 (7.14%)
occurrences (all)	2	7	5
Pain in extremity			
subjects affected / exposed	4 / 38 (10.53%)	6 / 80 (7.50%)	2 / 42 (4.76%)
occurrences (all)	5	10	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	4	6	2

Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	5 / 80 (6.25%)	4 / 42 (9.52%)
occurrences (all)	2	7	5
Herpes simplex			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	2	5	3
Conjunctivitis			
subjects affected / exposed	3 / 38 (7.89%)	3 / 80 (3.75%)	0 / 42 (0.00%)
occurrences (all)	4	4	0
Rhinitis			
subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)	4 / 80 (5.00%)	3 / 42 (7.14%)
occurrences (all)	1	4	3
Upper respiratory tract infection			
subjects affected / exposed	3 / 38 (7.89%)	6 / 80 (7.50%)	3 / 42 (7.14%)
occurrences (all)	3	10	7
Skin infection			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Urinary tract infection			
subjects affected / exposed	3 / 38 (7.89%)	7 / 80 (8.75%)	4 / 42 (9.52%)
occurrences (all)	10	15	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 38 (23.68%)	15 / 80 (18.75%)	6 / 42 (14.29%)
occurrences (all)	18	25	7
Dehydration			
subjects affected / exposed	3 / 38 (7.89%)	4 / 80 (5.00%)	1 / 42 (2.38%)
occurrences (all)	4	5	1
Fluid overload			
subjects affected / exposed	0 / 38 (0.00%)	3 / 80 (3.75%)	3 / 42 (7.14%)
occurrences (all)	0	4	4
Hyperglycaemia			

subjects affected / exposed	2 / 38 (5.26%)	2 / 80 (2.50%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Hyperkalaemia			
subjects affected / exposed	1 / 38 (2.63%)	4 / 80 (5.00%)	3 / 42 (7.14%)
occurrences (all)	1	4	3
Hyperuricaemia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	5	3
Hypokalaemia			
subjects affected / exposed	7 / 38 (18.42%)	13 / 80 (16.25%)	6 / 42 (14.29%)
occurrences (all)	10	16	6
Hypocalcaemia			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	2	4	2
Hypomagnesaemia			
subjects affected / exposed	2 / 38 (5.26%)	4 / 80 (5.00%)	2 / 42 (4.76%)
occurrences (all)	2	4	2
Hyponatraemia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 80 (3.75%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Hypophosphataemia			
subjects affected / exposed	4 / 38 (10.53%)	5 / 80 (6.25%)	1 / 42 (2.38%)
occurrences (all)	4	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2010	The rationale for this amendment was to correct inconsistencies within the protocol and to provide clarifications on timing of study procedures. Moreover, the amendment was intended to provide clarification on exclusion criterion number 8 and to provide further details on study procedures.
24 October 2011	Collect preliminary efficacy data of panobinostat at the recommended phase II dose (RPIID) level in conjunction with azacytidine (5-Aza/) by introducing a randomized, two-arm, open-label expansion phase, which determines the Phase IIb part of the study.
29 May 2012	Global amendment to provide guidance on dose adjustments for panobinostat and/or 5-Aza in the event of hematological toxicity, in particular thrombocytopenia and neutropenia as well as in the event of non-hematological toxicity for subjects enrolled in the Phase IIb part.
31 August 2012	Country-specific, non-substantial amendment for the Republic of Korea to clarify that the dose adjustment recommendations are for panobinostat and 5-Aza. The Korean Health Authority had given full approval for amendment 3, however requested to make the above mentioned changes prior to starting enrollment in Korea.
18 November 2016	The rationale of this amendment was to ensure treatment access for the patients that were still on treatment after the interim CSR data cut-off with a limited data collection. Therefore, for the patients ongoing treatment the study focused on collecting continuously Adverse Events, Serious Adverse Events, Concomitant Medications, and Dose Administration Records information. In addition, information (date and reason) related to End of Treatment and Study Evaluation Completion, date of disease progression as well as Survival information was to be provided. All other assessments were performed at the discretion of the investigators.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: