Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Panobinostat

Trial Indication(s)

Panobinostat, in combination with bortezomib and dexamethasone is indicated for the treatment of patients with relapsed or relapsed-and-refractory multiple myeloma who received at least one prior therapy.

Protocol Number

CLBH589D2308

Protocol Title

A multicenter, randomized, double blind, placebo controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

Clinical Trial Phase

Phase 3

Phase of Drug Development

III

Study Start/End Dates

Study Start Date: December 2009 (Actual)
Interim Report Date February-2014
Study Completion Date: July 2015 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multi-center, multinational, randomized, double-blind, placebo-controlled, parallel-group, Phase III trial of oral panobinostat or placebo in combination with intravenous bortezomib and low-dose oral dexamethasone. The target population was comprised of patients with relapsed or relapsed/refractory multiple myeloma having received one to three prior lines of therapy, and who were not refractory to bortezomib. All patients received study treatment until completion of Week 24 (eight 21-day cycles). Patients with clinical benefit (achieving ≥ No Change at Cycle 8 Day 1, as assessed per modified European group for blood and marrow transplantation [mEBMT] criteria) could continue study treatment up to Week 48 (four additional 42-day cycles). No crossover was allowed. The primary objective was to compare progression-free survival (PFS) between treatment arms. The key secondary objective was to compare the overall survival (OS) between the treatment arms.

Centers

Randomized patient Study center(s):
194 centers in 34 countries; Argentina (3 centers), Australia (6 centers), Austria (2 centers), Belgium (3 centers), Brazil (8 centers), Canada (4 centers), China (11 centers), Czech Republic (3 centers), Denmark (5 centers), Egypt (2 centers), Finland (2 centers), France (9 centers), Germany (17 centers), Greece (2 centers), Hong Kong (3 centers), Israel (2 centers), Italy (11 centers), Japan (14 centers), Korea (10 centers), Lebanon (1 center), Mexico (1 center), Netherlands (3 centers), Norway (3 centers), Poland (2 centers), Russia (2 centers), Singapore (1 center), South Africa (2 centers), Spain (10 centers), Sweden (5 centers), Taiwan (4 centers), Thailand (4 centers), Turkey (3 centers), United Kingdom (6 centers), United States (28 centers).

Participating center(s):
233 centers in 34 countries: South Africa(3), United States(41), Taiwan(4), Turkey(3), Thailand(4), Sweden(6), Singapore(1), Russia(2), Poland(3), Norway(6), Netherlands(5), Mexico(2), Lebanon(2), Korea, Republic of(10), Japan(14), Italy(13), Israel(4), Hong Kong(3), Greece(2), United Kingdom(8), France(11), Finland(2), Spain(10), Egypt(2), Denmark(5), Germany(23), Czech Republic(3), China(11), Canada(5), Brazil(8), Belgium(3), Austria(3), Australia(8), Argentina(3)

Publication (reference):
San-Miguel JF, Hungria VTM, Yoon SS, et al. (2014) Randomized, double-blind, placebo-controlled phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma (PANORAMA 1). Haematologica; 99(1):219-220.

Richardson PG, Hungria VTM, Yoon SS, et al (2014) Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol; 32(5s):8510.

San-Miguel JF, Hungria VT, Yoon SS, et al (2014) Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol; 15(11):1195-206.

San-Miguel JF, Hungria VT, Yoon SS, et al (2015) Final Analysis of overall survival from the phase 3 panorama 1 trial of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. ASH 57th annual meeting abstract 3026 (available upon request).

Richardson PG, Hungria VT, Yoon SS, et al (2015) Panobinostat plus bortezomib and dexamethasone in relapsed/relapsed and refractory myeloma: outcomes by prior treatment. Blood; 2016 Feb 11;127(6):713-21

Objectives:

- The primary objective was to compare progression-free survival (PFS) in patients treated with panobinostat in combination with bortezomib/dexamethasone vs. patients treated with placebo in combination with bortezomib/dexamethasone.
- The key secondary objective was to compare overall survival between treatment arms.

Additional secondary efficacy objectives

- To compare overall response rate (ORR) comprising complete response (CR), near CR (nCR) and partial response (PR)
- To compare nCR plus CR rate
- To compare minimal response rate
- To compare time to response
- To compare time to progression
- To assess duration of response from first occurrence of PR or better
- To assess safety of the combination therapy
- To assess health-related quality of life and symptoms of multiple myeloma
- To evaluate the pharmacokinetics of panobinostat and bortezomib in a subset of Japanese patients

Test Product (s), Dose(s), and Mode(s) of Administration

Panobinostat
Panobinostat/matching placebo was supplied as 5 mg, 15 mg, or 20 mg hard gelatin capsules. Panobinostat was given on a flat scale of 20 mg 3 times a week for two consecutive weeks (on a days 1,3,5,8,10,12) followed by a week off. The capsules of 5 mg and 15 mg were used for dose reductions only. The capsules were packaged in high density polyethylene bottles. All study drug (PAN/Placebo) was supplied by Novartis Drug Supply Management with each study drug in identically-appearing packaging.

Bortezomib
Bortezomib (Velcade®) is a commercially available product that was prescribed by the

Investigator. If required, bortezomib was supplied by the Novartis Country Pharmaceutical Organization to the investigational sites or reimbursed locally. In countries where bortezomib had not been approved for the study indication or corresponding treatment regimen, or if required by local regulations, Novartis provided bortezomib to the investigational sites. Prior to use, the contents of each vial was reconstituted and handled according to the manufacturer's instructions. The dose of bortezomib was 1.3 mg/m^2 administered as a 3 to 5 second bolus IV injection. In cycles 1-8 (3 weeks each) bortezomib was administered twice a week on the day .1,4,8 and 11, followed by a 10-day rest period. In cycles 9-12 (6 weeks each) bortezmib was administered once a week on days 1,8,22,and 29.

Dexamethasone

Dexamethasone was sourced locally by each investigational site. Dexamethasone is a generic medicine and is supplied in a variety of tablet strengths depending on the manufacturer. If required, Novartis reimbursed the Investigator for dexamethasone, and if required by local regulations dexamethasone was provided locally by the Novartis Country Pharmaceutical Organization. Dexamethasone was administered as single daily oral dose of 20 mg, on days of and after bortezomib administration.

Statistical Methods

All efficacy analyses were performed on the Full Analysis Set (FAS, all randomized patients). Safety Set patients (all patients who received at least one dose of any component of study treatment) were analyzed as treated. The Per Protocol Set (PP Set) was comprised of all patients from the FAS without any major protocol deviations.

Primary Efficacy Analyses: The primary analysis of PFS was done with a stratified log rank test considering a cumulative type I error rate of α=0.05, 2-sided. The HR for the treatment effect of PAN+ BTZ + Dex over PBO + BTZ + Dex was estimated and its 2-sided 95% CIs were reported. The estimation was based on a proportional hazards model with treatment and the two randomization strata used as stratification factors. Survivorship functions were estimated using the Kaplan-Meier product-limit method. The 25th, 50th (median) and 75th

percentile of PFS and 2-sided 95% CIs were reported for both treatment arms
Key Secondary Efficacy Analyses: OS was only tested if the primary endpoint of PFS was statistically significant. Irrespective of whether OS was tested or not, alpha for OS was spent according to the OS group sequential plan at each PFS analysis.
Secondary Efficacy Analyses: The estimated ORR along with corresponding 2-sided 95% exact CIs as derived by the Clopper-Pearson method were presented by treatment arm. ORR was analyzed using Cochran-Mantel-Haenszel test based on strata at randomization.
The nCR/CR rate and MR rate were provided with corresponding 2-sided 95% exact CIs as derived by the Clopper-Pearson method by treatment arm.
The median TTR and its 2-sided 95% CI were calculated for each treatment arm. This analysis included all patients in the FAS. Patients who had a PFS event (either progressed, relapsed or died due to any cause) and who did not experience CR, nCR or PR were censored at maximum follow-up (i.e. first patient-last visit to last patient-last visit used for the analysis) or at the last adequate response assessment. The 25th, 50th (median), and 75th percentiles of the TTR and the 2-sided 95% CIs were reported for both treatment arms.
Survivorship functions were estimated using the Kaplan-Meier product-limit method. Patients who did not experience progressive disease/relapse and were still alive were censored at the last adequate response assessment. DOR was analyzed based on data from responders (CR, nCR, or PR per mEBMT criteria based on investigator’s assessment) in the FAS.
Summary statistics and change from baseline analyses were provided for all scales/subscales of the EORTC QLQ-C30, QLQ-MY20, and FACT/GOG-NTX..
Safety: All AEs recorded during the study were listed and summarized. AEs were summarized

via treatment group by presenting the number and percentage of patients having at least one AE and for each preferred term using MedDRA coding. A patient with multiple occurrences of an AE was counted only once in the respective AE category and a patient with multiple CTC grades for an AE category was summarized under the maximum CTC grade recorded for the event for this patient. AE summaries were presented by primary system organ class, preferred term, and maximum CTC grade. In the summaries presented by grade, all AEs were pooled regardless of whether they are CTC-gradable or not, i.e., regardless of whether the question “CTCAE” on the AE CRF is answered ‘Yes’ or ‘No’. AE summaries included all treatment-emergent AEs and AEs with suspected relationship to study treatment.
Deaths reportable as serious AEs (SAEs) and non-fatal SAEs were listed by patient and tabulated by treatment arm and AE type.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Patient has a previous diagnosis of multiple myeloma.
2. Patient requires retreatment for multiple myeloma
3. Patient has measurable M component in serum or urine at study screening

Exclusion Criteria:
1. Patient who has progressed under all prior lines of anti MM therapy
2. Patient who has been treated by bortezomib before, and did not reach at least a minor response under this therapy, or progressed under it or within 60 days of last dose
3. Patient has shown intolerance to bortezomib or to dexamethasone or components of these drugs or has any contraindication to one or the other drug , following locally applicable prescribing information
4. Patient received prior treatment with DAC inhibitors including panobinostat
5. Patient has impaired cardiac function, or a prolonged QTc interval at screening ECG
6. Patient taking medications with relative risk of prolonging the QT interval or inducing Torsade de pointes

7. Female patient who is pregnant or breast feeding or with childbearing potential and not willing to use a double method of contraception up to 3 months after the end of study treatment. Male patient who is not willing to use a barrier method of contraception up to 3 months after the end of study treatment.

Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow Table

Overall Study

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Started	387	381
Completed	102[1]	102[1]
Not Completed	285[1]	279[1]
Abnormal test procedure results	3	8
Administrative problems	2	1
Adverse Event	130	66
Death	21	17
Disease progression	82	153
New Cancer therapy	4	7
Protocol Violation	3	4
Untreated	5	5

Lost to Follow-up	1	0
Withdrawal by Subject	34	18

[1] completed all planned cycles of study treatment as per protocol

Baseline Characteristics

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone	Total
Number of Participants [units: participants]	387	381	768
Age Continuous (units: years) Mean ± Standard Deviation	62.4±9.34	61.8±9.43	62.1±9.38
Gender, Male/Female (units: participants)			
Female	185	176	361
Male	202	205	407
Race/Ethnicity, Customized (units: Participants)			
Caucasian	249	250	499
Asian	128	104	232
Black	5	17	22
Other	5	10	15

Summary of Efficacy

The study met its primary objective; superiority was demonstrated for the PAN+BTZ+Dex arm over the PBO+BTZ+Dex arm for the primary analysis of PFS by investigator assessment based on mEBMT criteria. The HR (0.63, 95% CI: 0.52, 0.76); this result was statistically significant (p<0.0001). A clinically meaningful 3.9-month prolongation in median PFS was observed for the PAN+BTZ+Dex arm, from 8.1 months for those receiving PBO+BTZ+Dex to 12.0 months for patients receiving PAN+BTZ+Dex.
In the final OS analysis, OS was not statistically significantly different between the two treatment groups (p=0.5435, log-rank test, two-sided with critical alpha level = 0.0475) with a hazard ratio of 0.94 (95% CI: 0.78, 1.14). At the final analysis of OS, a lower proportion of deaths was reported in the PAN+BTZ+Dex arm (52.7%) as compared to the PBO+BTZ+Dex arm (55.4%). The median OS (95% CI) was 40.3 months (35.0, 44.8) and 35.8 months (29.0, 40.6), respectively

Primary Outcome Result(s)

Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
Progression-free survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination	207	260

with bortezomib and dexamethasone.
(units: number of events)

Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
Progression Free Survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. (units: months) Median (95% Confidence Interval)	11.99 (10.32 to 12.94)	8.80 (7.56 to 9.23)

Secondary Outcome Result(s)

Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
Final analysis of overall survival events in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone (units: Number of OS events)	204	211

Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants	387	381

Analyzed [units: participants]		
Final analysis of overall survival in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone (units: months) Median (95% Confidence Interval)	40.28 (35.02 to 44.81)	35.78 (28.98 to 40.64)

Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
Overall response rate in patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. (units: % participants with response)	60.7	54.6

Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
Time to response per investigator assessment (mEBMT criteria) of response patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. (units: months) Median (95% Confidence Interval)	1.51 (1.41 to 1.64)	2.00 (1.61 to 2.79)

Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units:	235	208

participants]		
Duration of response per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. (units: duration of response in months) Median (95% Confidence Interval)	13.14 (11.76 to 14.92)	10.87 (9.23 to 11.76)

Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone.

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381

Time to progression/relapse per investigator assessment (mEBMT criteria) patients treated with panobinostat in combination with bortezomib and dexamethasone vs. patients treated by placebo in combination with bortezomib and dexamethasone. (units: months) Median (95% Confidence Interval)	12.71 (11.30 to 14.06)	8.54 (7.66 to 9.72)

Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group

	Panobinostat + Bortezomib + Dexamethasone	**Placebo + Bortezomib + Dexamethasone**
Number of Participants Analyzed [units: participants]	387	381
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) Change from Baseline by treatment group (units: score on a scale) Least Squares Mean (95% Confidence Interval)		
Neurotoxicity wk 12 change baseline (n=212,240)	-4.481 (-5.33 to -3.63)	-3.337 (-4.17 to -2.50)
Neurotoxicity wk 24 change baseline (n=148,174)	-4.564 (-5.49 to -3.64)	-4.739 (-5.61 to -3.86)
Neurotoxicity wk 48	-3.158	-2.133

change baseline (n=35,26)	(-4.52 to -1.79)	(-3.64 to -0.627)
Physical wellbeing wk 12 chge (n=215,240)	-3.29 (-3.94 to -2.64)	-1.952 (-2.58 to -1.32)
Physical wellbeingwk 24 chge (n=150,176)	-3.044 (-3.74 to -2.35)	-2.259 (-2.92 to -1.60)
Physical wellbeing wk 48 chge (n=38,26)	-2.037 (-3.08 to -0.992)	0.203 (-1.03 to 1.439)
Trial Outcomes wk 12 chge (n=209,236)	-10.573 (-12.3 to -8.86)	-6.874 (-8.55 to -5.19)
Trial Outcomes wk 24 chge (n=148,173)	-9.84 (-11.7 to -7.98)	-8.894 (-10.7 to -7.13)
Trial Outcomes wk 48 chge (n=35,26)	-6.633 (-9.28 to -3.98)	-2.821 (-5.76 to 0.122)
FACT-G Total wk 12 chge (n=213,240)	-6.658 (-8.23 to -5.09)	-4.106 (-5.64 to -2.57)
FACT-G Total wk 24 chge (n=147,175)	-6.076 (-7.84 to -4.31)	-4.609 (-6.30 to -2.92)
FACT-G Total wk 48 chge (n=37,26)	-2.704 (-5.29 to -0.118)	-1.435 (-4.42 to 1.547)
FACT/GOGNTX Total wk 12 chge (n=206,230)	-11.176 (-13.3 to -9.03)	-7.524 (-9.64 to -5.41)
FACT/GOGNTX Total wk 24 chge (n=146,172)	-10.581 (-12.9 to -8.23)	-9.179 (-11.4 to -6.93)
FACT/GOGNTX Total wk 48 chge (n=35,26)	-5.871 (-9.24 to -2.50)	-3.151 (-6.92 to 0.614)
Functional Well-being chge wk 12 (n=213,241)	-2.56 (-3.16 to -1.96)	-1.60 (-2.18 to -1.03)
Functional Well-being chge wk 24 (n=150,176)	-2.40 (-3.08 to -1.72)	-2.06 (-2.70 to -1.42)
Functional Well-being chge wk 48 (n=38,26)	-1.21 (-2.25 to -0.17)	-1.01 (-2.20 to 0.18)
Social/Family Well-being	-0.58	-0.73

chge wk 12 (n=215,240)	(-1.12 to -0.04)	(-1.24 to -0.21)
Social/Family Well-being chge wk 24 (n=151,176)	-0.53 (-1.15 to 0.10)	-0.24 (-0.83 to 0.35)
Social/Family Well-being chge wk 48 (n=38,26)	-0.75 (-1.57 to 0.08)	-0.73 (-1.66 to 0.19)
Emotional Well-being chge wk 12 (n=208,237)	-0.02 (-0.49 to 0.44)	0.36 (-0.09 to 0.81)
Emotional Well-being chge wk 24 (n=147,173)	0.01 (-0.50 to 0.52)	0.21 (-0.28 to 0.69)
Emotional Well-being chge wk 48 (n=37,26)	1.09 (0.28 to 1.90)	0.06 (-0.87 to 0.99)

European Organization for Research and Treatment of Cancer Multiple Myeloma Module(EORTC QLQ-MY20) -Change from Baseline by treatment group

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
European Organization for Research and Treatment of Cancer Multiple Myeloma Module(EORTC QLQ-MY20) -Change from Baseline by treatment group (units: score on a scale) Least Squares Mean (95% Confidence Interval)		
Disease Symptom wk 12 change baseline (n=215,243)	-4.795 (-6.76 to -2.83)	-4.865 (-6.75 to -2.98)
Disease Symptom wk 24 change baseline (n=148,177)	-4.401 (-6.53 to -2.27)	-6.797 (-8.79 to -4.81)
Disease Symptom wk 48 change baseline (n=37,26)	-2.836 (-6.76 to 1.084)	-6.626 (-11.1 to -2.12)
Side effects of treatment	8.162	5.524

wk 12 chge (n=213,242)	(6.510 to 9.814)	(3.933 to 7.115)
Side effects of treatment wk 24 chge (n=148,175)	9.016 (6.955 to 11.08)	7.731 (5.795 to 9.668)
Side effects of treatment wk 48 chge (n=37,26)	3.357 (0.442 to 6.273)	3.654 (0.352 to 6.956)
Future perspective wk 12 chge (n=214,242)	5.319 (2.893 to 7.744)	6.194 (3.854 to 8.533)
Future perspective wk 24 chge (n=148,176)	3.877 (0.977 to 6.778)	5.839 (3.103 to 8.575)
Future perspective wk 48 chge (n=37,26)	4.331 (-.142 to 8.804)	6.951 (1.807 to 12.10)
Body image wk 12 chge (n=213,240)	-7.178 (-10.5 to -3.87)	-6.22 (-9.41 to -3.03)
Body image wk 24 chge (n=147,175)	-11.463 (-15.3 to -7.66)	-7.358 (-10.9 to -3.81)
Body image wk 48 chge (n=37,26)	-2.161 (-7.73 to 3.410)	-4.666 (-11.1 to 1.729)

European Organization for Research and Treatment of Cancer Quality of Life Questionaire : EORTC QLQ-C30 - Summary Statistics by treatment group

	Panobinostat + Bortezomib + Dexamethasone	Placebo + Bortezomib + Dexamethasone
Number of Participants Analyzed [units: participants]	387	381
European Organization for Research and Treatment of Cancer Quality of Life Questionaire : EORTC QLQ-C30 - Summary		

Statistics by treatment group
(units: score on a scale)
Least Squares Mean (95% Confidence Interval)

Global health wk 12 change baseline (n=216,239)	-9.853 (-12.50 to -7.20)	-4.044 (-6.60 to -1.49)
Global health wk 24 change baseline (n=150,176)	-7.867 (-10.7 to -5.08)	-1.518 (-4.11 to 1.075)
Global health wk 48 change baseline (n=38,26)	-2.986 (-7.21 to 1.237)	4.345 (-0.416 to 9.106)
Physical functioning wk 12 chge (n=217,242)	-9.67 (-12.00 to -7.38)	-5.393 (-76.3 to -3.16)
Physical functioning wk 24 chge (n=151,177)	-9.516 (-12.20 to -6.86)	-6.456 (-8.98 to -3.93)
Physical functioning wk 48 chge (n=38,26)	-2.88 (-6.41 to 0.651)	2.037 (-2.07 to 6.147)
Role functioning wk 12 chge (n=215,237)	-11.159 (-14.6 to -7.74)	-6.762 (-10.1 to -3.45)
Role functioning wk 24 chge (n=150,176)	-11.875 (-15.7 to -8.01)	-11.263 (-14.9 to -7.61)
Role functioning wk 48 chge (n=38,26)	-5.927 (-11.4 to -0.424)	-0.401 (-6.73 to 5.924)
Cognitive functioning wk 12 chge (n=216,240)	-4.464 (-6.89 to -2.04)	-1.023 (-3.36 to 1.318)
Cognitive functioning wk 24 chge (n=149,176)	-6.053 (-8.87 to -3.24)	-3.542 (-6.22 to -0.865)
Cognitive functioning wk 48 chge (n=38,26)	-5.568 (-9.79 to -1.34)	-4.042 (-8.99 to 0.902)
Social functioning wk 12 chge (n=216,240)	-8.502 (-11.6 to -5.44)	-3.991 (-6.97 to 1.02)
Social functioning wk 24 chge (n=148,171)	-8.925 (-12.4 to -5.42)	-6.338 (-9.66 to -3.02)

Social functioning wk 48 chge (n=37,26)	-6.104 (-11.0 to -1.22)	4.617 (-0.930 to 10.16)
Fatigue wk 12 chge (n=217,241)	15.122 (12.27 to 17.98)	7.939 (5.174 to 10.70)
Fatigue wk 24 chge (n=151,176)	12.677 (9.419 to 15.94)	9.203 (6.136 to 12.27)
Fatigue wk 48 chge(n=38,26)	4.646 (0.086 to 9.206)	-2.625 (-7.88 to 2.628)
Dyspnea wk 12 chge (n=217,240)	13.964 (10.60 to 17.33)	6.266 (3.012 to 9.521)
Dyspnea wk 24 chge (n=151,177)	7.939 (4.639 to 11.24)	5.308 (2.221 to 8.394)
Dyspnea wk 48 chge (n=38,26)	4.118 (-1.58 to 9.813)	2.82 (-3.88 to 9.523)
Insomnia wk 12 chge (n=216,239)	6.283 (2.851 to 9.715)	7.625 (4.331 to 10.92)
Insomnia wk 24 chge (n=149,176)	10.023 (6.038 to 14.01)	6.104 (2.381 to 9.827)
Insomnia wk 48 chge (n=38,26)	-2.464 (-8.74 to 3.811)	-3.442 (-10.9 to 4.017)
Appetite loss wk 12 chge (n=217,239)	15.167 (11.60 to 18.74)	5.383 (1.925 to 8.841)
Appetite loss wk 24 chge (n=151,176)	16.574 (12.39 to 20.76)	5.861 (1.918 to 9.804)
Appetite loss wk 48 chge (n=38,26)	3.999 (-2.08 to 10.07)	-2.963 (-9.99 to 4.061)
Constipation wk 12 chge (n=215,240)	4.135 (0.667 to 7.603)	6.42 (3.104 to 9.735)
Constipation wk 24 chge (n=151,177)	-0.153 (-3.64 to 3.337)	0.524 (-2.73 to 3.782)
Constipation wk 48 chge (n=38,25)	-0.358 (-5.57 to 4.851)	-0.946 (-7.26 to 5.373)

Diarrhea wk 12 chge (n=217,241)	18.888 (15.04 to 22.74)	10.206 (6.452 to 13.96)
Diarrhea wk 24 chge (n=150,177)	23.163 (18.46 to 27.87)	16.406 (11.98 to 20.83)
Diarrhea wk 48 chge (n=38,26)	20.48 (14.02 to 26.94)	10.996 (3.422 to 18.57)
Emotional function chge wk 12 (n=217,240)	-2.90 (-5.28 to -.52)	-0.40 (-2.72 to 1.92)
Emotional function chge wk 24 (n=150,176)	-2.26 (-4.90 to 0.37)	-0.28 (-2.77 to 2.22)
Emotional function chge wk 48 (n=38,26)	0.43 (-3.93 to 4.78)	4.09 (-0.97 to 9.15)
Nausea/vomiting chge wk 12 (n=217,239)	6.12 (4.00 to 8.24)	0.71 (-1.33 to 2.75)
Nausea/vomiting chge wk 24 (n=151,177)	4.07 (2.00 to 6.14)	0.42 (-1.54 to 2.38)
Nausea/vomiting chge wk 48 (n=38,26)	0.88 (-2.03 to 3.78)	-2.235 (-5.67 to 1.20)
Pain chge wk 12 (n= 217, 240)	-0.47 (-3.56 to 2.63)	0.82 (-2.18 to 3.82)
Pain chge wk 24 (n= 150, 175)	2.07 (-1.38 to 5.51)	-2.39 (-5.63 to 0.85)
Pain chge wk 48 (n= 38, 26)	-0.03 (-5.35 to 5.30)	-8.31 (-14.60 to -2.06)
Financial difficulties chge wk 12 (n=215,239)	-4.87 (-7.71 to -2.03)	-3.23 (-5.97 to -0.49)
Financial difficulties chge wk 24 (n=148,174)	-0.74 (-3.96 to 2.47)	-0.891 (-3.91 to 2.124)
Financial difficulties chge wk 48 (n=37,26)	-3.77 (-8.65 to 1.10)	-6.29 (-11.90 to -0.65)

Summary of Safety

No apparent new or unexpected safety signals were identified for panobinostat when used in combination with bortezomib and dexamethasone.

Safety Results

Serious Adverse Events by System Organ Class

Additional Description Adverse events were collected for the safety population, the participants who took at least one dose of the interventions.Efficacy analysis were performed on the FAS

	PAN+BTZ+Dex N = 381	PBO+BTZ+Dex N = 377
Total participants affected	228 (59.84%)	157 (41.64%)
Blood and lymphatic system disorders		
Anaemia[1, †]	14 (3.67%)	3 (0.80%)
Febrile neutropenia[1, †]	3 (0.79%)	1 (0.27%)
Hyperviscosity syndrome[1, †]	0 (0.00%)	1 (0.27%)
Leukocytosis[1, †]	1 (0.26%)	0 (0.00%)
Leukopenia[1, †]	2 (0.52%)	0 (0.00%)
Monocytosis[1, †]	1 (0.26%)	0 (0.00%)
Neutropenia[1, †]	2 (0.52%)	1 (0.27%)
Pancytopenia[1, †]	1 (0.26%)	1 (0.27%)
Thrombocytopenia[1, †]	28 (7.35%)	8 (2.12%)
Cardiac disorders		

Acute coronary syndrome[1, †]	1 (0.26%)	0 (0.00%)
Acute myocardial infarction[1, †]	1 (0.26%)	0 (0.00%)
Angina pectoris[1, †]	2 (0.52%)	2 (0.53%)
Atrial fibrillation[1, †]	4 (1.05%)	2 (0.53%)
Atrial flutter[1, †]	0 (0.00%)	1 (0.27%)
Bradycardia[1, †]	2 (0.52%)	0 (0.00%)
Cardiac arrest[1, †]	2 (0.52%)	2 (0.53%)
Cardiac failure[1, †]	1 (0.26%)	1 (0.27%)
Cardiac failure acute[1, †]	1 (0.26%)	0 (0.00%)
Cardiac failure congestive[1, †]	0 (0.00%)	1 (0.27%)
Cardiopulmonary failure[1, †]	0 (0.00%)	1 (0.27%)
Cardio-respiratory arrest[1, †]	0 (0.00%)	1 (0.27%)
Left ventricular dysfunction[1, †]	0 (0.00%)	1 (0.27%)
Myocardial infarction[1, †]	2 (0.52%)	0 (0.00%)
Myocardial ischaemia[1, †]	2 (0.52%)	0 (0.00%)
Pericardial effusion[1, †]	0 (0.00%)	1 (0.27%)
Sinus tachycardia[1, †]	1 (0.26%)	0 (0.00%)
Tachycardia[1, †]	2 (0.52%)	0 (0.00%)
Ventricular tachycardia[1, †]	1 (0.26%)	0 (0.00%)
Ear and labyrinth disorders		
Vertigo[1, †]	1 (0.26%)	0 (0.00%)

Eye disorders		
Conjunctivitis[1, †]	1 (0.26%)	0 (0.00%)
Exophthalmos[1, †]	1 (0.26%)	0 (0.00%)
Optic ischaemic neuropathy[1, †]	1 (0.26%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal discomfort[1, †]	1 (0.26%)	0 (0.00%)
Abdominal distension[1, †]	1 (0.26%)	0 (0.00%)
Abdominal pain[1, †]	3 (0.79%)	3 (0.80%)
Abdominal pain upper[1, †]	1 (0.26%)	0 (0.00%)
Colitis[1, †]	3 (0.79%)	0 (0.00%)
Constipation[1, †]	3 (0.79%)	3 (0.80%)
Diarrhoea[1, †]	43 (11.29%)	9 (2.39%)
Dysphagia[1, †]	1 (0.26%)	0 (0.00%)
Faecaloma[1, †]	1 (0.26%)	0 (0.00%)
Gastric haemorrhage[1, †]	2 (0.52%)	0 (0.00%)
Gastritis[1, †]	2 (0.52%)	0 (0.00%)
Gastrointestinal haemorrhage[1, †]	2 (0.52%)	3 (0.80%)
Gastrooesophageal reflux disease[1, †]	1 (0.26%)	0 (0.00%)
Haematemesis[1, †]	1 (0.26%)	0 (0.00%)
Haematochezia[1, †]	2 (0.52%)	0 (0.00%)
Haemorrhoids[1, †]	0 (0.00%)	1 (0.27%)
Ileus[1, †]	5 (1.31%)	3 (0.80%)
Ileus paralytic[1, †]	0 (0.00%)	1 (0.27%)

Inguinal hernia[1, †]	2 (0.52%)	1 (0.27%)
Intestinal ischaemia[1, †]	1 (0.26%)	0 (0.00%)
Large intestine perforation[1, †]	1 (0.26%)	0 (0.00%)
Nausea[1, †]	7 (1.84%)	0 (0.00%)
Necrotising oesophagitis[1, †]	1 (0.26%)	0 (0.00%)
Pancreatitis[1, †]	1 (0.26%)	0 (0.00%)
Pancreatitis acute[1, †]	2 (0.52%)	1 (0.27%)
Peritoneal necrosis[1, †]	1 (0.26%)	0 (0.00%)
Rectal haemorrhage[1, †]	1 (0.26%)	0 (0.00%)
Subileus[1, †]	1 (0.26%)	1 (0.27%)
Upper gastrointestinal haemorrhage[1, †]	2 (0.52%)	0 (0.00%)
Vomiting[1, †]	12 (3.15%)	3 (0.80%)
General disorders and administration site conditions		
Asthenia[1, †]	15 (3.94%)	6 (1.59%)
Chest discomfort[1, †]	1 (0.26%)	1 (0.27%)
Chills[1, †]	1 (0.26%)	0 (0.00%)
Fatigue[1, †]	11 (2.89%)	2 (0.53%)
General physical health deterioration[1, †]	2 (0.52%)	0 (0.00%)
Generalised oedema[1, †]	1 (0.26%)	0 (0.00%)
Hypothermia[1, †]	0 (0.00%)	2 (0.53%)
Multi-organ failure[1, †]	1 (0.26%)	1 (0.27%)
Non-cardiac chest pain[1, †]	1 (0.26%)	3 (0.80%)

Oedema peripheral[1, †]	1 (0.26%)	0 (0.00%)
Pyrexia[1, †]	16 (4.20%)	11 (2.92%)
Spinal pain[1, †]	0 (0.00%)	1 (0.27%)
Sudden death[1, †]	1 (0.26%)	1 (0.27%)
Hepatobiliary disorders		
Biliary dyskinesia[1, †]	0 (0.00%)	1 (0.27%)
Cholecystitis[1, †]	1 (0.26%)	1 (0.27%)
Hepatic cirrhosis[1, †]	1 (0.26%)	0 (0.00%)
Hepatic failure[1, †]	1 (0.26%)	0 (0.00%)
Hepatomegaly[1, †]	1 (0.26%)	1 (0.27%)
Hyperbilirubinaemia[1, †]	0 (0.00%)	1 (0.27%)
Jaundice[1, †]	0 (0.00%)	1 (0.27%)
Infections and infestations		
Acute tonsillitis[1, †]	1 (0.26%)	0 (0.00%)
Appendicitis[1, †]	1 (0.26%)	0 (0.00%)
Aspergillosis[1, †]	1 (0.26%)	0 (0.00%)
Aspergillus infection[1, †]	1 (0.26%)	0 (0.00%)
Atypical pneumonia[1, †]	1 (0.26%)	0 (0.00%)
Bacteraemia[1, †]	0 (0.00%)	1 (0.27%)
Bacteriuria[1, †]	1 (0.26%)	0 (0.00%)
Bronchitis[1, †]	3 (0.79%)	2 (0.53%)
Bronchopneumonia[1, †]	1 (0.26%)	1 (0.27%)
Bronchopulmonary aspergillosis[1, †]	1 (0.26%)	0 (0.00%)
Cellulitis[1, †]	2 (0.52%)	1 (0.27%)

Clostridium difficile colitis[1, †]	2 (0.52%)	0 (0.00%)
Cytomegalovirus colitis[1, †]	1 (0.26%)	0 (0.00%)
Device related infection[1, †]	0 (0.00%)	1 (0.27%)
Device related sepsis[1, †]	1 (0.26%)	0 (0.00%)
Disseminated tuberculosis[1, †]	1 (0.26%)	0 (0.00%)
Diverticulitis[1, †]	1 (0.26%)	0 (0.00%)
Enteritis infectious[1, †]	1 (0.26%)	0 (0.00%)
Erysipelas[1, †]	0 (0.00%)	1 (0.27%)
Escherichia urinary tract infection[1, †]	0 (0.00%)	1 (0.27%)
Gastroenteritis[1, †]	7 (1.84%)	2 (0.53%)
Gastroenteritis salmonella[1, †]	2 (0.52%)	0 (0.00%)
Gastrointestinal infection[1, †]	1 (0.26%)	0 (0.00%)
Haemophilus sepsis[1, †]	0 (0.00%)	1 (0.27%)
Hepatitis B[1, †]	3 (0.79%)	1 (0.27%)
Herpes zoster[1, †]	4 (1.05%)	5 (1.33%)
Infection[1, †]	5 (1.31%)	2 (0.53%)
Influenza[1, †]	1 (0.26%)	1 (0.27%)
Lobar pneumonia[1, †]	2 (0.52%)	0 (0.00%)
Lower respiratory tract infection[1, †]	3 (0.79%)	3 (0.80%)
Lung infection[1, †]	2 (0.52%)	2 (0.53%)
Nasopharyngitis[1, †]	0 (0.00%)	1 (0.27%)

Necrotising fasciitis[1, †]	0 (0.00%)	2 (0.53%)
Neutropenic sepsis[1, †]	2 (0.52%)	1 (0.27%)
Oral candidiasis[1, †]	0 (0.00%)	1 (0.27%)
Parotitis[1, †]	1 (0.26%)	0 (0.00%)
Periodontitis[1, †]	1 (0.26%)	0 (0.00%)
Pharyngitis[1, †]	2 (0.52%)	1 (0.27%)
Pneumococcal sepsis[1, †]	1 (0.26%)	0 (0.00%)
Pneumonia[1, †]	56 (14.70%)	40 (10.61%)
Pneumonia bacterial[1, †]	0 (0.00%)	2 (0.53%)
Pneumonia fungal[1, †]	2 (0.52%)	0 (0.00%)
Pneumonia haemophilus[1, †]	0 (0.00%)	1 (0.27%)
Pneumonia influenzal[1, †]	2 (0.52%)	1 (0.27%)
Pneumonia pneumococcal[1, †]	0 (0.00%)	1 (0.27%)
Pneumonia respiratory syncytial viral[1, †]	0 (0.00%)	1 (0.27%)
Pseudomonal bacteraemia[1, †]	1 (0.26%)	0 (0.00%)
Pulmonary tuberculosis[1, †]	1 (0.26%)	1 (0.27%)
Respiratory tract infection[1, †]	4 (1.05%)	2 (0.53%)
Salmonellosis[1, †]	0 (0.00%)	1 (0.27%)
Sepsis[1, †]	9 (2.36%)	7 (1.86%)
Septic shock[1, †]	9 (2.36%)	2 (0.53%)
Sinusitis[1, †]	1 (0.26%)	1 (0.27%)
Skin infection[1, †]	1 (0.26%)	0 (0.00%)

Staphylococcal sepsis[1, †]	0 (0.00%)	1 (0.27%)
Streptococcal sepsis[1, †]	0 (0.00%)	1 (0.27%)
Upper respiratory tract infection[1, †]	4 (1.05%)	3 (0.80%)
Urinary tract infection[1, †]	8 (2.10%)	4 (1.06%)
Varicella[1, †]	1 (0.26%)	0 (0.00%)
Viral haemorrhagic cystitis[1, †]	0 (0.00%)	1 (0.27%)
Viral infection[1, †]	1 (0.26%)	0 (0.00%)
Injury, poisoning and procedural complications		
Accidental overdose[1, †]	3 (0.79%)	0 (0.00%)
Ankle fracture[1, †]	1 (0.26%)	0 (0.00%)
Contusion[1, †]	0 (0.00%)	1 (0.27%)
Fall[1, †]	2 (0.52%)	0 (0.00%)
Femoral neck fracture[1, †]	1 (0.26%)	1 (0.27%)
Femur fracture[1, †]	0 (0.00%)	1 (0.27%)
Hand fracture[1, †]	1 (0.26%)	0 (0.00%)
Humerus fracture[1, †]	0 (0.00%)	1 (0.27%)
Intentional overdose[1, †]	1 (0.26%)	0 (0.00%)
Laceration[1, †]	1 (0.26%)	0 (0.00%)
Overdose[1, †]	3 (0.79%)	0 (0.00%)
Pelvic fracture[1, †]	1 (0.26%)	0 (0.00%)
Rib fracture[1, †]	0 (0.00%)	1 (0.27%)
Tibia fracture[1, †]	1 (0.26%)	0 (0.00%)
Transfusion reaction[1, †]	1 (0.26%)	0 (0.00%)

Investigations		
Alanine aminotransferase increased[1, †]	1 (0.26%)	1 (0.27%)
Aspartate aminotransferase increased[1, †]	1 (0.26%)	1 (0.27%)
Blood creatinine increased[1, †]	1 (0.26%)	2 (0.53%)
Blood lactate dehydrogenase increased[1, †]	0 (0.00%)	1 (0.27%)
Blood potassium decreased[1, †]	0 (0.00%)	1 (0.27%)
Blood pressure decreased[1, †]	0 (0.00%)	1 (0.27%)
C-reactive protein increased[1, †]	2 (0.52%)	0 (0.00%)
Gamma-glutamyltransferase increased[1, †]	0 (0.00%)	2 (0.53%)
General physical condition abnormal[1, †]	1 (0.26%)	0 (0.00%)
Platelet count decreased[1, †]	4 (1.05%)	0 (0.00%)
Weight decreased[1, †]	0 (0.00%)	1 (0.27%)
White blood cell count decreased[1, †]	1 (0.26%)	0 (0.00%)
Metabolism and nutrition disorders		
Acidosis[1, †]	0 (0.00%)	1 (0.27%)
Decreased appetite[1, †]	4 (1.05%)	2 (0.53%)

Dehydration[1, †]	11 (2.89%)	5 (1.33%)
Diabetes mellitus[1, †]	0 (0.00%)	1 (0.27%)
Diabetes mellitus inadequate control[1, †]	1 (0.26%)	0 (0.00%)
Electrolyte imbalance[1, †]	1 (0.26%)	0 (0.00%)
Hypercalcaemia[1, †]	1 (0.26%)	3 (0.80%)
Hyperglycaemia[1, †]	2 (0.52%)	3 (0.80%)
Hypocalcaemia[1, †]	1 (0.26%)	0 (0.00%)
Hypochloraemia[1, †]	1 (0.26%)	0 (0.00%)
Hypoglycaemia[1, †]	1 (0.26%)	2 (0.53%)
Hypokalaemia[1, †]	8 (2.10%)	4 (1.06%)
Hyponatraemia[1, †]	4 (1.05%)	1 (0.27%)
Hypophagia[1, †]	2 (0.52%)	0 (0.00%)
Hypophosphataemia[1, †]	1 (0.26%)	0 (0.00%)
Metabolic acidosis[1, †]	0 (0.00%)	1 (0.27%)
Tumour lysis syndrome[1, †]	1 (0.26%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia[1, †]	2 (0.52%)	0 (0.00%)
Back pain[1, †]	3 (0.79%)	2 (0.53%)
Bone pain[1, †]	1 (0.26%)	1 (0.27%)
Bursitis[1, †]	1 (0.26%)	0 (0.00%)
Flank pain[1, †]	1 (0.26%)	0 (0.00%)
Joint swelling[1, †]	1 (0.26%)	0 (0.00%)
Muscular weakness[1, †]	0 (0.00%)	1 (0.27%)
Musculoskeletal pain[1, †]	1 (0.26%)	1 (0.27%)

Myalgia[1, †]	2 (0.52%)	0 (0.00%)
Myopathy[1, †]	1 (0.26%)	0 (0.00%)
Osteonecrosis of jaw[1, †]	1 (0.26%)	0 (0.00%)
Pain in extremity[1, †]	1 (0.26%)	1 (0.27%)
Spinal pain[1, †]	0 (0.00%)	1 (0.27%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cancer pain[1, †]	0 (0.00%)	1 (0.27%)
Endometrial cancer[1, †]	1 (0.26%)	0 (0.00%)
Prostate cancer[1, †]	0 (0.00%)	1 (0.27%)
Rectal cancer[1, †]	0 (0.00%)	1 (0.27%)
Small cell lung cancer[1, †]	0 (0.00%)	2 (0.53%)
Nervous system disorders		
Altered state of consciousness[1, †]	1 (0.26%)	0 (0.00%)
Autonomic neuropathy[1, †]	1 (0.26%)	0 (0.00%)
Brain compression[1, †]	0 (0.00%)	1 (0.27%)
Brain injury[1, †]	0 (0.00%)	1 (0.27%)
Brain oedema[1, †]	1 (0.26%)	0 (0.00%)
Central nervous system haemorrhage[1, †]	0 (0.00%)	1 (0.27%)
Central nervous system necrosis[1, †]	1 (0.26%)	0 (0.00%)
Cerebral haemorrhage[1, †]	1 (0.26%)	2 (0.53%)
Cerebrovascular	3 (0.79%)	0 (0.00%)

accident[1, †]		
Coma[1, †]	1 (0.26%)	0 (0.00%)
Convulsion[1, †]	1 (0.26%)	0 (0.00%)
Cranial nerve paralysis[1, †]	0 (0.00%)	1 (0.27%)
Depressed level of consciousness[1, †]	1 (0.26%)	0 (0.00%)
Dizziness[1, †]	5 (1.31%)	2 (0.53%)
Haemorrhage intracranial[1, †]	1 (0.26%)	0 (0.00%)
Headache[1, †]	1 (0.26%)	0 (0.00%)
Hemiparesis[1, †]	1 (0.26%)	1 (0.27%)
Hyperreflexia[1, †]	0 (0.00%)	1 (0.27%)
Lacunar infarction[1, †]	1 (0.26%)	1 (0.27%)
Loss of consciousness[1, †]	5 (1.31%)	1 (0.27%)
Neuralgia[1, †]	1 (0.26%)	1 (0.27%)
Neuropathy peripheral[1, †]	3 (0.79%)	1 (0.27%)
Paraparesis[1, †]	1 (0.26%)	0 (0.00%)
Paraplegia[1, †]	0 (0.00%)	1 (0.27%)
Polyneuropathy[1, †]	0 (0.00%)	1 (0.27%)
Post herpetic neuralgia[1, †]	0 (0.00%)	1 (0.27%)
Sciatica[1, †]	0 (0.00%)	1 (0.27%)
Seizure[1, †]	1 (0.26%)	0 (0.00%)
Sensory loss[1, †]	0 (0.00%)	1 (0.27%)
Somnolence[1, †]	1 (0.26%)	0 (0.00%)
Speech disorder[1, †]	0 (0.00%)	1 (0.27%)

Syncope[1, †]	5 (1.31%)	2 (0.53%)
Transient ischaemic attack[1, †]	1 (0.26%)	0 (0.00%)
VIIth nerve paralysis[1, †]	0 (0.00%)	1 (0.27%)
Psychiatric disorders		
Confusional state[1, †]	1 (0.26%)	1 (0.27%)
Delirium[1, †]	1 (0.26%)	0 (0.00%)
Hypomania[1, †]	1 (0.26%)	0 (0.00%)
Mental disorder[1, †]	0 (0.00%)	1 (0.27%)
Mental status changes[1, †]	1 (0.26%)	0 (0.00%)
Renal and urinary disorders		
Acute kidney injury[1, †]	7 (1.84%)	9 (2.39%)
Anuria[1, †]	0 (0.00%)	1 (0.27%)
Azotaemia[1, †]	0 (0.00%)	1 (0.27%)
Oliguria[1, †]	1 (0.26%)	0 (0.00%)
Renal failure[1, †]	4 (1.05%)	4 (1.06%)
Renal failure acute[1, †]	7 (1.84%)	9 (2.39%)
Renal impairment[1, †]	1 (0.26%)	1 (0.27%)
Ureteric obstruction[1, †]	1 (0.26%)	0 (0.00%)
Reproductive system and breast disorders		
Benign prostatic hyperplasia[1, †]	1 (0.26%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		

Acute respiratory distress syndrome[1, †]	0 (0.00%)	2 (0.53%)
Acute respiratory failure[1, †]	3 (0.79%)	1 (0.27%)
Aspiration[1, †]	0 (0.00%)	1 (0.27%)
Asthma[1, †]	0 (0.00%)	1 (0.27%)
Chronic obstructive pulmonary disease[1, †]	0 (0.00%)	1 (0.27%)
Cough[1, †]	1 (0.26%)	0 (0.00%)
Dyspnoea[1, †]	4 (1.05%)	7 (1.86%)
Epistaxis[1, †]	2 (0.52%)	1 (0.27%)
Hypoventilation[1, †]	0 (0.00%)	1 (0.27%)
Hypoxia[1, †]	1 (0.26%)	0 (0.00%)
Lung disorder[1, †]	1 (0.26%)	1 (0.27%)
Lung infiltration[1, †]	1 (0.26%)	0 (0.00%)
Orthopnoea[1, †]	1 (0.26%)	1 (0.27%)
Pleural effusion[1, †]	4 (1.05%)	0 (0.00%)
Pneumonitis[1, †]	1 (0.26%)	3 (0.80%)
Pneumothorax[1, †]	1 (0.26%)	0 (0.00%)
Pulmonary embolism[1, †]	4 (1.05%)	4 (1.06%)
Pulmonary haemorrhage[1, †]	1 (0.26%)	0 (0.00%)
Pulmonary hypertension[1, †]	1 (0.26%)	0 (0.00%)
Pulmonary oedema[1, †]	1 (0.26%)	1 (0.27%)
Respiratory distress[1, †]	1 (0.26%)	0 (0.00%)
Respiratory failure[1, †]	5 (1.31%)	0 (0.00%)
Tachypnoea[1, †]	0 (0.00%)	1 (0.27%)

Skin and subcutaneous tissue disorders		
Acute febrile neutrophilic dermatosis[1, †]	1 (0.26%)	1 (0.27%)
Dermatitis allergic[1, †]	0 (0.00%)	1 (0.27%)
Rash[1, †]	2 (0.52%)	1 (0.27%)
Swelling face[1, †]	1 (0.26%)	0 (0.00%)
Vascular disorders		
Aortic stenosis[1, †]	1 (0.26%)	0 (0.00%)
Circulatory collapse[1, †]	2 (0.52%)	0 (0.00%)
Deep vein thrombosis[1, †]	2 (0.52%)	3 (0.80%)
Embolism[1, †]	1 (0.26%)	0 (0.00%)
Haematoma[1, †]	1 (0.26%)	0 (0.00%)
Hypotension[1, †]	5 (1.31%)	2 (0.53%)
Hypovolaemic shock[1, †]	3 (0.79%)	0 (0.00%)
Lymphoedema[1, †]	0 (0.00%)	1 (0.27%)
Orthostatic hypotension[1, †]	9 (2.36%)	1 (0.27%)
Shock haemorrhagic[1, †]	1 (0.26%)	0 (0.00%)
Venous thrombosis limb[1, †]	1 (0.26%)	1 (0.27%)

† Systematic Assessment
1 MedDRA

Other Adverse Events by System Organ Class

Additional Description	Adverse events were collected for the safety population, the participants who took at least one dose of the interventions. Efficacy analysis were performed on the FAS
Frequent Event Reporting Threshold	5%

	PAN+BTZ+Dex N = 381	PBO+BTZ+Dex N = 377
Total participants affected	379 (99.48%)	366 (97.08%)
Blood and lymphatic system disorders		
Anaemia[1, †]	154 (40.42%)	125 (33.16%)
Leukopenia[1, †]	61 (16.01%)	31 (8.22%)
Lymphopenia[1, †]	52 (13.65%)	35 (9.28%)
Neutropenia[1, †]	112 (29.40%)	40 (10.61%)
Thrombocytopenia[1, †]	238 (62.47%)	150 (39.79%)
Eye disorders		
Conjunctivitis[1, †]	28 (7.35%)	31 (8.22%)
Gastrointestinal disorders		
Abdominal distension[1, †]	30 (7.87%)	25 (6.63%)
Abdominal pain[1, †]	50 (13.12%)	38 (10.08%)
Abdominal pain upper[1, †]	43 (11.29%)	36 (9.55%)
Constipation[1, †]	101 (26.51%)	122 (32.36%)
Diarrhoea[1, †]	254 (66.67%)	155 (41.11%)
Dyspepsia[1, †]	47 (12.34%)	43 (11.41%)
Nausea[1, †]	137 (35.96%)	78 (20.69%)
Vomiting[1, †]	91 (23.88%)	47 (12.47%)
General disorders and administration site conditions		
Asthenia[1, †]	77 (20.21%)	51 (13.53%)
Fatigue[1, †]	155 (40.68%)	109 (28.91%)

Oedema peripheral[1, †]	108 (28.35%)	72 (19.10%)
Pyrexia[1, †]	90 (23.62%)	48 (12.73%)
Infections and infestations		
Bronchitis[1, †]	20 (5.25%)	25 (6.63%)
Herpes zoster[1, †]	15 (3.94%)	36 (9.55%)
Nasopharyngitis[1, †]	49 (12.86%)	46 (12.20%)
Respiratory tract infection[1, †]	17 (4.46%)	20 (5.31%)
Upper respiratory tract infection[1, †]	65 (17.06%)	53 (14.06%)
Urinary tract infection[1, †]	23 (6.04%)	15 (3.98%)
Investigations		
Alanine aminotransferase increased[1, †]	22 (5.77%)	19 (5.04%)
Blood creatinine increased[1, †]	37 (9.71%)	21 (5.57%)
Blood urea increased[1, †]	20 (5.25%)	10 (2.65%)
Platelet count decreased[1, †]	43 (11.29%)	17 (4.51%)
Weight decreased[1, †]	44 (11.55%)	17 (4.51%)
Metabolism and nutrition disorders		
Decreased appetite[1, †]	106 (27.82%)	46 (12.20%)
Hyperglycaemia[1, †]	30 (7.87%)	25 (6.63%)
Hypoalbuminaemia[1, †]	21 (5.51%)	8 (2.12%)
Hypocalcaemia[1, †]	35 (9.19%)	32 (8.49%)
Hypokalaemia[1, †]	100 (26.25%)	52 (13.79%)

Hyponatraemia[1, †]	48 (12.60%)	18 (4.77%)
Hypophosphataemia[1, †]	42 (11.02%)	32 (8.49%)
Musculoskeletal and connective tissue disorders		
Arthralgia[1, †]	25 (6.56%)	26 (6.90%)
Back pain[1, †]	45 (11.81%)	46 (12.20%)
Bone pain[1, †]	21 (5.51%)	31 (8.22%)
Muscle spasms[1, †]	23 (6.04%)	21 (5.57%)
Muscular weakness[1, †]	24 (6.30%)	20 (5.31%)
Myalgia[1, †]	24 (6.30%)	24 (6.37%)
Pain in extremity[1, †]	40 (10.50%)	54 (14.32%)
Nervous system disorders		
Dizziness[1, †]	67 (17.59%)	61 (16.18%)
Dysgeusia[1, †]	36 (9.45%)	26 (6.90%)
Headache[1, †]	51 (13.39%)	40 (10.61%)
Hypoaesthesia[1, †]	28 (7.35%)	34 (9.02%)
Neuralgia[1, †]	38 (9.97%)	44 (11.67%)
Neuropathy peripheral[1, †]	117 (30.71%)	133 (35.28%)
Paraesthesia[1, †]	24 (6.30%)	27 (7.16%)
Peripheral sensory neuropathy[1, †]	42 (11.02%)	46 (12.20%)
Polyneuropathy[1, †]	28 (7.35%)	28 (7.43%)
Psychiatric disorders		
Insomnia[1, †]	73 (19.16%)	61 (16.18%)
Respiratory, thoracic and mediastinal		

disorders		
Cough[1, †]	81 (21.26%)	70 (18.57%)
Dyspnoea[1, †]	53 (13.91%)	40 (10.61%)
Productive cough[1, †]	18 (4.72%)	19 (5.04%)
Skin and subcutaneous tissue disorders		
Rash[1, †]	33 (8.66%)	23 (6.10%)
Vascular disorders		
Hypertension[1, †]	27 (7.09%)	23 (6.10%)
Hypotension[1, †]	49 (12.86%)	34 (9.02%)
Orthostatic hypotension[1, †]	22 (5.77%)	11 (2.92%)

† Systematic Assessment
1 MedDRA

Conclusion:

The study met its primary objective; superiority was demonstrated for the panobinostat arm over the placebo arm for the primary analysis of PFS by investigator assessment. The estimated HR (0.63, 95% CI: 0.52, 0.76); this result was statistically significant (p<0.0001). A clinically meaningful 3.9-month prolongation in median PFS was observed for the panobinostat arm, from 8.1 months for patients receiving placebo to 12.0 months for those receiving panobinostat. For this final analysis, OS was not statistically significantly different between the two treatment groups. Treatment with panobinostat was also associated with numerically higher rates of overall response relative to placebo (60.7% vs. 54.6%, respectively). Additionally, the nCR/CR rate was almost two-fold higher in the PAN+BTZ+Dex arm vs. the PBO+BTZ+Dex arm, 27.9% vs. 15.7%, respectively. The clinical benefit for PAN+BTZ+Dex also includes a median DoR of 13.1 months (vs. 10.9 months for PBO+BTZ+Dex) and TTP of 12.7 months (vs. 8.5 months for PBO+BTZ+Dex). The efficacy results from this trial demonstrate that panobinostat in combination with bortezomib/dexamethasone provides a meaningful and robust clinical benefit in patients with relapsed or relapsed-and-refractory multiple myeloma. The clinical benefit with respect to PFS, ORR and DOR compares favorably with that of current standard-of-care regimens in this patient population.

The AEs/SAEs reported in each treatment group are consistent with the known safety and tolerability profiles of panobinostat and bortezomib. Overlapping toxicities for panobinostat and bortezomib (thrombocytopenia, neutropenia, diarrhea, and fatigue) were drivers for the safety profile observed with the panobinostat/bortezomib/dexamethasone treatment regimen. No apparent new or unexpected safety signals were identified for panobinostat.

Date of Clinical Trial Report

1/19/2016.