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Clinical Development

Panobinostat / LBH589 / Farydak®

LBH589D2408

Panobinostat Post Authorization Safety Study, a non-interventional study of panobinostat in combination with bortezomib and dexamethasone in patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

Document type: Abbreviated Clinical Study Report

Development phase: IV

1 Study information

Study title: Panobinostat Post Authorization Safety Study, a non-interventional study of panobinostat in combination with bortezomib and dexamethasone in patients with Relapsed and/or Refractory Multiple Myeloma (RRMM).

Test drug/investigational product: Panobinostat (LBH589)

Indication studied: Relapsed and/or refractory multiple myeloma

Sponsor: Novartis

Protocol identification: LBH589D2408

EU PAS register number: EUPAS18261; 09-Jan-2016

Development phase of study: IV

Study initiation date: 02-May-2017 (first patient first visit)

Study completion date: 31-Mar-2019 (last patient last visit)

Principal or Coordinating Investigator(s): Not applicable

Company/Sponsor signatory: [redacted], MD, Novartis Pharma AG, E. Hanover, USA

Statement: This study was conducted in compliance with Good Clinical Practice (GCP).

Report date(s): 29-Nov-2019 (content final)

Earlier reports from the same study: None

2 Synopsis

Name of product: Panobinostat

Study number: LBH589D2408

EU PAS register number: EUPAS18261; 09-Jan-2016

Title of study: Panobinostat Post Authorization Safety Study, a non-interventional study of panobinostat in combination with bortezomib and dexamethasone in patients with Relapsed and/or Refractory Multiple Myeloma (RRMM).

Investigator(s): Not applicable

Study center(s): Germany (3 sites), Greece (4 sites)

Publication (reference): None

Study period

Study initiation date: 02-May-2017 (first subject first visit)

Study completion date: 31-Mar-2019 (last subject last visit)

Phase of development (phase of this clinical study): IV

Objectives:

Primary objectives

- To collect safety data in patients with relapsed and/or refractory multiple myeloma treated with panobinostat in combination with bortezomib and dexamethasone in a real-world setting, according to the current EU prescribing information.
- To document the adherence to the dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events. The effectiveness of the additional risk minimization measures “i.e. compliance card and blister pack” is assessed through specific data collection.

Secondary objectives

- To document the incidence and outcome of the adverse events which are contained within the Risk Management Plan.
- To document new adverse event occurrence and PAN+BTZ+DEX treatment regimen dose modification due to adverse event in special populations, including but not limited to:
  - Elderly patients (above 65 years)
  - Patients with renal impairment
  - Patients with hepatic impairment

Methodology: This was a Post Authorization Safety Study according to the EU Volume 9a of the Rules of Governing Medicinal Products in the European Union and was planned as a prospective, multicenter, multi-national non-interventional study based on primary data collection for patients diagnosed with RRMM. This study did not impose a therapy protocol, therapeutic interventions or a visit schedule. At study entry, patients had a new or ongoing panobinostat treatment (in combination with bortezomib and dexamethasone) in accordance with the local (country-specific) panobinostat prescribing information.

The recruitment of the 425 patients was expected to occur over a period of three years depending on the reimbursement process in the European countries and subsequent product launch. Because of the nature of the study there was no intent to assess the overall survival or any efficacy endpoint. However, the survival data (deaths due to any causes) were collected for the purpose of safety analysis.

Number of subjects (planned and analyzed): A total of approximately 425 subjects were planned for this study, however, only 20 subjects were treated due to early termination of the study as the recruitment of subjects was challenging due to changes in treatment preferences.

Diagnosis and main criteria for inclusion: The target population included adult patients with a diagnosis of relapsed and/or refractory multiple myeloma. Any patients irrespective of age, previous treatment, Eastern Cooperative Oncology Group status, living in one of the EEA countries could be entered in the protocol as soon as they had received at least one dose of panobinostat and treated according to the EU SmPC.

Inclusion criteria were:

- Patients diagnosed with relapsed and/or refractory multiple myeloma
- Patients had a new or ongoing treatment with a regimen of PAN+BTZ+DEX according to the EU approved SmPC.
- Patients were eligible to enter the study at any time during the first 12 cycles and no later than Day 1 of Cycle 13.

Duration of treatment: The overall study duration (first patient first visit to last patient last visit) was expected to be six years, allowing all patients an observation period of 48 weeks for the PAN+BTZ+DEX treatment period, and a follow-up period of 24 months for second primary malignancy, survival and record for new antineoplastic treatments. The median duration of exposure to treatment with PAN+BTZ+Dex was 5.14 weeks (range: 1.14 to 48.71 weeks). The majority of subjects (60.0%) was treated shorter than eight weeks; one subjects was treated between 48 and 64 weeks.

Test and reference therapies, dose and mode of administration: According to SmPC, the recommended starting dose of panobinostat was 20 mg, taken orally once a day, on Days 1, 3, 5, 8, 10 and 12 of a 21-day cycle in combination with bortezomib and dexamethasone. Patients were to be treated initially for eight cycles. It was recommended that patients with clinical benefit continue the treatment for eight additional cycles. The total duration of PAN+BTZ+DEX treatment could be up to 16 cycles (48 weeks).

Recommended dose of bortezomib (1.3 mg/m^2 given as an injection) is twice weekly for the first 8 cycles and once a week for the following cycles.

The recommended dose of dexamethasone was 20 mg taken orally on a full stomach four times per week for the first 8 cycles and twice a week for the following cycles.

Panobinostat, bortezomib, and dexamethasone were all obtained from commercial sources.

No reference therapy was administered.

Criteria for evaluation

Efficacy: This PASS was designed as a non-interventional study with primary data collection to describe the safety profile of the triple combination in real world use. Efficacy measurements were not applicable.

Safety: The study collected safety data during the PAN+BTZ+DEX treatment period in order to characterize treatment emergent adverse events and their management. Medication errors were documented during the PAN+BTZ+DEX treatment period. The effectiveness of the additional risk minimization measures “i.e. compliance card and blister pack” were assessed through specific data collection during the PAN+BTZ+DEX treatment period. Second primary malignancy, survival and record for new antineoplastic treatments were documented until completion of the 24 months follow up period.

For all patients adverse events (serious and non-serious) were collected during PAN+BTZ+DEX treatment period, plus an additional 30 days collection of safety data.

The incidence and outcome of the adverse events as described in the secondary objective was documented.

Statistical methods:

The following primary variables were summarized as follows:

- The proportions of patients with AEs/SAEs, discontinuation due to AE, and on-treatment deaths were provided.
- Counts, and proportions of patients with medication errors (i.e. dose omission and improper dose (under dose, overdose, and extra dose) were provided.
- The proportion of patients who have AE due to medication errors will be provided. In addition to this, severity of AEs due to medication errors were also summarized descriptively.
- The proportion of patients with overdose associated with SAEs were provided.
- The proportions of patients, using the compliance card, who came at the visit with compliance card and who fully completed the compliance card were also provided.
- Results on HCP and patients survey regarding the use of compliance card and blister pack were also summarized and reported.

The following secondary variables were summarized as follows:

- To evaluate the incidence and outcome of adverse events contained within the risk management plan.
- To document new adverse event occurrence and PAN+BTZ+DEX treatment regimen dose modification due to adverse event in special populations.

Summary - Results

Demographic and background characteristics: The median age of the subjects was 62.5 years (range: 38 to 83 years) with nine subjects ≥ 65 years. All subjects were Caucasian with 13 subjects belonging to Other ethnicity (missing for 7 subjects); 11 subjects (55.0%) were male and nine subjects (45.0%) female. The median body mass index was 24.2 kg/m^2 (range: 20.3 to 36.2 kg/m^2).

Efficacy results: This was a non-interventional study with primary data collection to describe the safety profile of the triple combination in real world use. No efficacy assessments were performed.

Safety results:

- The median duration of exposure to treatment with PAN+BTZ+Dex was 5.14 weeks (range: 1.14 to 48.71 weeks). The median duration of exposure to treatment with panobinostat was 4.79 weeks (range: 0.57 to 48.71 weeks).
- Seventeen subjects used and fully completed the compliance card. Two subjects had medication errors i.e. omission or improper dose (under dose, overdose, and extra dose)
- All subjects had at least one AE. Most subjects had an AE in the system organ class of blood and lymphatic disorders (55.0%), followed by general disorders and administration site conditions (40.0%), infections and infestations (40.0%), and gastrointestinal disorders (30.0%).
- The most frequently occurring AE was thrombocytopenia in nine subjects (45.0%) followed by fatigue (5 subjects, 25.0%), and anemia and pyrexia (4 subjects each, 20.0%).
- Three subjects (15.0%) died on-treatment due to study indication.
- Eight subjects had an SAE of whom six subjects had a grade 3/4 SAE.

Conclusion:

- Due to early termination of the study, the number of subjects is too low to draw any conclusion.
- No new safety signals observed outside the approved registration study.

Date of report: 29-Nov-2019 (content final)

3 Table of Contents

4 List of abbreviations and definition of terms

AE	Adverse event
BTZ	Bortezomib
Dex	Dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
PAN	Panobinostat
PASS	Post authorization safety study
RRMM	Relapsed and/or refractory multiple myeloma
SAE	Serious adverse event
SOC	System organ class

5 Ethics

5.1 Independent Ethics Committee or Institutional Review Board

The study protocol was reviewed by the Independent Ethics Committee or Institutional Review Board for each center, as listed in Appendix 16.1.3.

5.2 Ethical conduct of the study

The study was conducted according to ICH E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki.

5.3 Patient information and consent

Informed consent was obtained from each patient in writing before any study specific procedure was performed. The study was described to the patient by the investigator or designee, who answered any questions, and written information was also provided.

Samples of the written information given to each patient and the consent form are presented in Appendix 16.1.3.

6 Investigators and study administrative structure

The administrative structure of the study, including internal and external participants, is described in Appendix 16.1.4-Section 1.

A list of investigators, their affiliations and their qualifications, plus that of other important staff is provided in Appendix 16.1.4-Section 2.

Novartis staff analyzed this study and authored this report. The signatures of the principal or coordinating investigator, the sponsor's responsible medical officer, and the report authors are provided in Appendix 16.1.5.

7 Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells, which accounts for 10% to 15% of all hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow in adults. Approximately 20,500 people in Europe received a new diagnosis of MM in 2012 (Ferlay et al 2013). Despite survival improvements from 45 to 60 months after the introduction of newer therapies, particularly proteasome inhibitors and immunomodulatory drugs, often used in combination with dexamethasone, no curative treatment is available and MM ultimately progresses to fatal outcome.

Excessive proliferation of malignant plasma cells leads in most cases myeloma cells to produce monoclonal proteins comprised of immunoglobulin or components of immunoglobulin. The hallmarks of MM are bone marrow failure, renal failure, and lytic bone disease. Signs of bone marrow dysfunction include anemia, leukopenia leading to increased susceptibility to infection, and decreased platelet counts with attendant susceptibility to bleeding. Patients suffer from bone pain and fractures as a result of osteolytic lesions and complications of renal failure which

further contribute to worsening anemia. These signs and symptoms are commonly denoted by the acronym CRAB for (Calcium elevation, Renal dysfunction, Anemia, Bone destruction).

Panobinostat (PAN) is a pan deacetylase inhibitor. The US and EU Marketing Authorization (granted by the FDA in Feb 2015 and the EMA in Aug-2015) for panobinostat are supported by data from a large positive global Phase 3 randomized controlled trial (PANORAMA 1) where panobinostat was added to the prevailing standard of care regimen (bortezomib and dexamethasone (BTZ+Dex)) .This study demonstrated a significant improvement in PFS of 3.9 months compared to BTZ+Dex+ placebo (HR 0.63). This 37% reduction in risk of progression or death is considered clinically relevant by the treating community.

The most frequent adverse events (AEs) with the combination of PAN+BTZ+Dex included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting) and constitutional disorders. The rate of grade 3/4 thrombocytopenia was higher in the PAN+BTZ+Dex arm than the placebo (PBO+BTZ+Dex) arm (57% vs 24.9%). Thrombocytopenia could be managed in the majority of patients with dose and/or schedule modifications of both PAN and BTZ. GI toxicities were the most commonly reported organ toxicities in the PAN+BTZ+Dex arm and were mostly due to AEs of G3/4 diarrhea (25.5%), nausea (5.5%), vomiting (7.3%). About 5% of patients with GI AEs discontinued treatment due to diarrhea suggesting that these AEs could be effectively managed by interventions such as dose adjustments or interruptions, or antidiarrheal medications.

At the time of the EU Marketing Authorization, granted by the European Commission (EC) in Aug-2015, the Pharmacovigilance Risk Assessment Committee (PRAC) requested to perform a Post Authorization Safety Study (PASS) as part of RMP PAC (categorized as category 3) with the following objectives.

1. Collect real-world safety data on the use of the triplet-combination of panobinostat and bortezomib and dexamethasone.

2. Document adherence to dosing regimen and frequency and clinical implications of medication errors.

8 Study objectives

8.1 Primary objective(s)

- To collect safety data in patients with relapsed and/or refractory multiple myeloma treated with panobinostat in combination with bortezomib and dexamethasone in a real-world setting, according to the current EU prescribing information.
- To document the adherence to the dosing regimen (including the dosing card, blister pack) by describing clinical characteristics, frequency and severity of the medication error events. The effectiveness of the additional risk minimization measures “i.e. compliance card and blister pack” is assessed through specific data collection.

8.2 Secondary objectives

To document the incidence and outcome of the following adverse events which are contained within the Risk Management Plan:

- Severe diarrhea
- Cardiac toxicity including :QTc prolongation, and ischemic heart disease
- Severe hemorrhage
- Severe infections (including sepsis and pneumonia)
- Ischemic colitis
- Reactivation of hepatitis B
- Venous thromboembolism
- Hypothyroidism
- Second primary malignancies
- Hepatic dysfunction
- Renal dysfunction

To document new adverse event occurrence and PAN+BTZ+Dex treatment regimen dose modification due to adverse event in special populations, including but not limited to:

- Elderly patients (above 65 years)
- Patients with renal impairment
- Patients with hepatic impairment

9 Investigational plan

9.1 Study design

This was a Post Authorization Safety Study according to the EU Volume 9a of the Rules of Governing Medicinal Products in the European Union and was planned as a prospective, multicenter, multi-national non-interventional study based on primary data collection for patients diagnosed with RRMM. This study did not impose a therapy protocol, therapeutic interventions or a visit schedule. At study entry, patients had a new or ongoing panobinostat treatment (in combination with bortezomib and dexamethasone) in accordance with the local (country-specific) panobinostat prescribing information. The protocol was approved by PRAC in September 2016 as RMP post Approval Commitment.

The recruitment of the planned 425 patients was expected to occur over a period of three years depending on the reimbursement process in the European countries and subsequent product launch. Austria, Greece, Belgium, Germany, France, Italy, Norway, Spain, Sweden, Romania already confirmed their participation to this PASS. However, only Germany and Greece have recruited 21 patients in total, and the study was terminated early. The overall study duration (first patient first visit to last patient last visit) was expected to be six years, allowing all patients an observation period of 48 weeks for the PAN+BTZ+Dex treatment period, and a follow-up period of 24 months for second primary malignancy, survival and record for new antineoplastic treatments.

Because of the nature of the study, there was no intent to assess the overall survival or any efficacy endpoint. However, the survival data (deaths due to any causes) were collected for the purpose of safety analysis. The enrollment was defined as the patient entry into the study; the point at which informed consent was obtained.

The baseline was defined as the point in time when the patient signed the informed consent.

A patient was considered evaluable if he/she had received at least one dose of PAN+BTZ+Dex treatment.

9.2 Population

The target population included adult patients with a diagnosis of relapsed and/or refractory multiple myeloma in line with the approved EU SmPC.

Any patients irrespective of age, previous treatment, Eastern Cooperative Oncology Group status, living in one of the EEA countries could be enrolled in the study as soon as they had received at least one dose of panobinostat and were treated according to the EU SmPC.

9.2.1 Inclusion criteria

1. Patients diagnosed with relapsed and/or refractory multiple myeloma
2. Patients had a new or ongoing treatment with a regimen of PAN+BTZ+Dex according to the EU approved SmPC.
3. Patients were eligible to enter the study at any time during the first 12 cycles and no later than Day 1 of Cycle 13.

9.2.2 Exclusion criteria

1. Patients not providing informed consent
2. Patients participating concurrently in an investigational study involving panobinostat or another anti-myeloma drug.

9.3 Study treatments

9.3.1 Drug medication of interest

Panobinostat treatment had to follow the EU approved SmPC.

According to SmPC, the recommended starting dose of panobinostat was 20 mg, taken orally once a day, on Days 1, 3, 5, 8, 10 and 12 of a 21-day cycle. Patients were to be treated initially for eight cycles. It was recommended that patients with clinical benefit had to continue the treatment for eight additional cycles. The total duration of PAN+BTZ+Dex treatment could be up to 16 cycles (48 weeks, Appendix 16.1.1-Table 7-1 and Appendix 16.1.1-Table 7-2).

Panobinostat was administered in combination with bortezomib and dexamethasone. The bortezomib and dexamethasone prescribing information was to be consulted prior to the start of the combination treatment to assess whether a dose reduction was required.

Recommended dose of bortezomib (1.3 mg/m^2 given as an injection) is twice weekly for the first 8 cycles and once a week for the following cycles.

The recommended dose of dexamethasone was 20 mg taken orally on a full stomach four times per week for the first 8 cycles and twice a week for the following cycles.

Physician could adapt dose and/or schedule according to patient condition or treatment tolerance as per their current practice and following the EU approved SmPC.

9.3.2 Identity of investigational products

Panobinostat, bortezomib, and dexamethasone were all obtained from commercial sources.

9.3.3 Selection of dose(s)

Panobinostat treatment had to follow the EU approved SmPC.

9.3.4 Permitted dose adjustments and interruptions of study treatment

Dose adjustments and/or interruptions due to adverse events were tabulated and listed.

9.3.5 Concomitant treatment

Concomitant or prior medications were entered into the database and summarized by descriptive statistics.

9.3.6 Discontinuation of study treatment and premature patient withdrawal

For patients who discontinue prematurely, the reason for discontinuation was determined and documented.

9.3.7 Study completion and post-study treatment

The study was to be completed when each of the 425 patients had either withdrawn from the study or completed maximum three years of observation period including a maximum of 48 weeks of PAN+BTZ+Dex treatment period and two years of follow up period whichever occurred earlier. Due to recruitment challenge, only 21 patients were enrolled and the study was terminated early.

9.3.8 Treatment accountability and compliance

9.3.8.1 Treatment accountability

Each patient was assigned a patient number. The physician or designated staff contacted the Interactive Response Technology and provided the requested identifying information for the patient to register them into the Interactive Response Technology. Once assigned, the Patient Number could not be reused for any other patient and the Patient Number for that individual could not be changed, even if the patient was re-screened.

Treatment with PAN+BTZ+Dex was at the discretion of the investigator in accordance with the local (country-specific) prescribing information.

9.3.8.2 Treatment compliance

Compliance is part of the primary objective. Compliance cards are provided to the patients.

Detailed information about the compliance cards is provided in Appendix 16.1.1-Section 7.4 and Appendix 16.1.1-Annex 3.

9.3.9 Early study termination

Following severe recruitment issues due to various factors, including lack of reimbursement, change of therapeutic landscape for the Treatment of MM in the EU, a variation seeking to remove the conduct of the mentioned PASS study from the RMP was submitted to CHMP.

On 14-Feb-2019, the Committee for Medicinal Products for Human Use (CHMP) provided a positive opinion to remove the commitment to conduct the PASS study CLBH589D2408, listed as category 3 study in the RMP. Thereafter the PASS study was early terminated and the last recorded patient visit in the clinical database has been fixed on the 12-Apr-2019.

9.4 Study assessments

9.4.1 Visit schedule

The study visits and procedures are presented in Appendix 16.1.1-Table 7-3 which lists all of the assessments and indicates with an "X" the visits at which they were performed.

9.4.2 Efficacy assessments

This PASS was designed as a non-interventional study with primary data collection to describe the safety profile of the triple combination in real world use. Efficacy measurements were not applicable.

9.4.3 Safety assessments

The study collected safety data during the PAN+BTZ+Dex treatment period in order to characterize treatment emergent adverse events and their management. Medication errors were documented during the PAN+BTZ+Dex treatment period. The effectiveness of the additional risk minimization measures "i.e. compliance card and blister pack" were assessed through specific data collection during the PAN+BTZ+Dex treatment period. Second primary malignancy, survival and record for new antineoplastic treatments were documented until completion of the 24 months follow up period.

For all patients adverse events (serious and non-serious) were collected during PAN+BTZ+Dex treatment period, plus additional 30 days following the end of treatment.

The incidence and outcome of the adverse events as described in the secondary objective (Section 8.2) was documented.

During the PAN+BTZ+Dex treatment period, only laboratory abnormalities that resulted in AEs/serious adverse events (SAEs) were recorded. Laboratory abnormalities that did not meet the criteria of clinical significance, as judged by the physician, were not to be reported as adverse events.

9.4.4 Assessment of medication errors

ICH definition of medication errors is very broad and currently there is no information to evaluate the nature, pattern, and frequency of medication errors that could occur in the post-marketing setting. This study will report on dosing errors for panobinostat (i.e. dose omission and improper dose: overdose, under dose, extra dose) and their clinical outcome.

9.4.5 Appropriateness of safety assessments

This was a single arm study without comparison and the rationale for the design was as follows:

Novartis evaluated the possibility to conduct this research through a registry or choosing a specific comparator. Novartis excluded these two options based on the following reasons:

1. The main purpose of this study was to collect safety data and to document patient adherence to the dosing regimen as part of the primary objective once panobinostat was available on the market.
2. In addition, there was no standard of care that could be used as a meaningful comparator and the enrolment period was significantly prolonged if the study enrolled a sufficient number of patients with a specific alternative treatment to be used as a comparator.

Therefore, the design of this PASS was appropriate and in line with the primary objectives of the study.

Novartis carefully ensured that the PASS did not interfere/modify the local medical practices. The sites were selected based on their multiple myeloma treatment experience and patients were enrolled even if they already started being treated for their multiple myeloma indication. Novartis interacted with local networks to ensure targeting the best representativeness as possible. Therefore, no limitation of potential selection bias was expected in this trial.

The limitations of the research method was mainly due to the fact that there was no planned visit schedule and no systematic collection of data.

9.5 Data quality assurance

For details related to site monitoring and data quality assurance see Appendix 16.1.1-Section 7.15.

9.6 Statistical methods

9.6.1 Data analysis

Details of the data analysis section are provided in Appendix 16.1.9.

9.6.2 Analysis sets

The Screened Set (SCR) consists of all patients who signed the ICF.

The Full Analysis Set comprises all patients who received at least one dose of treatment during the study.

The Safety Set comprises all patients who received at least one dose of treatment during the study. The Safety Set will be used for all safety evaluations.

The Full Analysis Set and Safety Set are identical in this study.

9.6.3 Patient disposition, demographics and other baseline characteristics

Demographics and other baseline data and disease characteristics were summarized descriptively using the Full Analysis Set.

9.6.4 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Duration of exposure was summarized descriptively. In addition, the duration of exposure was categorized into time intervals; frequency counts and percentages were presented for the number (%) of patients in each interval.

Patient level listings of all doses administered on treatment along with dose change reasons were produced.

The safety set was used for all summaries and listings of study treatment.

Duration of exposure to study treatment was considered by taking into account the duration of exposure to the investigational drug and combination partner:

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

Duration of exposure to investigational drug (days) = (last date of exposure to investigational drug) – (date of first administration of investigational drug) + 1.

9.6.5 Analysis of the primary endpoint(s)

9.6.5.1 Variable

The following primary variables were summarized as follows:

- The proportions of patients with AEs/SAEs, discontinuation due to AE, and on-treatment deaths were provided.
- Counts, and proportions of patients with medication errors (i.e. dose omission and improper dose (under dose, overdose, and extra dose) were provided.
- The proportion of patients who have AE due to medication errors were provided. In addition to this, severity of AEs due to medication errors were also summarized descriptively.
- The proportion of patients with overdose associated with SAEs were provided.
- The proportions of patients, using the compliance card, who came at the visit with compliance card and who fully completed the compliance card were also provided.
- Results on HCP and patients survey regarding the use of compliance card and blister pack were also summarized and reported.

9.6.5.2 Statistical hypothesis, model, and method of analysis

No statistical hypotheses was tested in this study.

9.6.6 Analysis of secondary endpoint(s)

- To evaluate the incidence and outcome of adverse events contained within the risk management plan.
- To document new adverse event occurrence and PAN+BTZ+Dex treatment regimen dose modification due to adverse event in special populations:
    - elderly patients (above 65 years)

- patients with renal impairment
- patients with hepatic impairment.

9.6.7 Safety

Analyses were done on the safety set.

The overall observation period was divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- Post-treatment period: starting at day 31 after last dose of study medication.

9.6.7.1 Adverse events

AE summaries included all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page were listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period were flagged in the listings.

AEs were summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE was counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term was summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade was included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class was presented alphabetically and the preferred terms was sorted within primary SOC in descending frequency.

The following adverse event summaries were produced; overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy.

9.6.7.2 Deaths

Separate summaries for on-treatment and all deaths were produced. All deaths were listed, post treatment deaths were flagged.

9.6.8 Sample size calculation

As this is a post-market observational study, the sample size is a simple estimate and no formal sample size calculation was performed.

A total of approximately 425 patients (385 evaluable patients, defined as receiving at least one dose of PAN+BTZ+Dex treatment) were planned for this study, allowing a margin of error of 5% with 95% confidence for estimating the incidence rate of AEs, assuming 10% dropout rate.

The observed incidence rates of adverse events which were contained within the RMP in the treatment arm PAN+BTZ+Dex in CLBH589D2308 PANORAMA-1 study were with wide

variations from 1% to 68%. Capturing this maximum variability of the estimates, the sample size in this study was based on an assumed AE incidence rate of 50%.

Furthermore, statistical computations were performed (Appendix 16.1.1-Table 7-5) to evaluate probabilities to detect at least one patient with an AE given 385 evaluable patients and different scenarios of AE incidence rates (Hanley and Lippman-Hand 1983). For example, there is 95% probability of observing at least one patient with an adverse event that has a true probability of occurrence of 0.8%.

9.6.9 Interim analysis

Interim safety updates (AEs, SAEs, medication errors from Novartis Argus database) as part of the PSURs have been performed. Interim updates on the adherence to dosing regimen were reported on a yearly basis and included in the PSURs.

On request of the PRAC, an unplanned interim analysis was conducted using 01-Jun-2018 as cut-off date when 19 patients were enrolled.

9.7 Changes in the conduct of the study or planned analyses

9.7.1 Protocol amendments

There were no amendments to the protocol.

9.7.2 Other changes in study conduct

The study was terminated early based on CHMP Opinion endorsing the removal of the PASS study commitment.

9.7.3 Changes in planned analysis

With only 21 out of originally planned 425 patients enrolled into the study, only key safety outputs were prepared for an abbreviated CSR, which included:

- Medication errors and use of compliance card
- AEs/SAEs regardless of study drug relationship
- AEs/SAEs suspected to be study drug related
- AEs leading to study drug discontinuation
- AEs requiring dose adjustment or study drug interruption
- AEs requiring significant additional therapy
- AEs of special interest regardless of study drug relationship
- On treatment deaths and all deaths on study
- Hematology, vital signs, and ECG were listed

10 Study patients

10.1 Disposition of patients

Twenty of the 21 enrolled patients were treated and they all discontinued treatment; the reasons for treatment discontinuation included progressive disease (9 patients, 42.9%), adverse event (8 patients, 38.1%), and patient/guardian decision (3 patients, 14.3%) (Table 10-1).

Eight patients were followed for study evaluation, and they completed study evaluation due to death (6 patients, 28.6%) and study terminated by the sponsor (2 patients, 9.5%).

Table 10-1 Patient disposition (Screened set)

Disposition Reason	PAN+BTZ+Dex N=21 n (%)
Patients enrolled	21 (100.0)
Patients treated	20 (95.2)
End of treatment	20 (95.2)
Primary reason for end of treatment	
Adverse event	8 (38.1)
Progressive disease	9 (42.9)
Patient/guardian decision	3 (14.3)
Study evaluation after end of treatment	
Patients no longer being followed for study evaluation	12 (57.1)
Patients continuing to be followed for study evaluation	8 (38.1)
Primary reason for study evaluation completion	
Death	6 (28.6)
Study terminated by sponsor	2 (9.5)

- Patients who have completed treatment duration per protocol may have switched to commercial drug.
Source: Table 14.1-1.1

10.2 Protocol deviations

There were no protocol deviations (Table 14.1-2.1).

10.3 Data sets analyzed

The screened set contained 21 patients, while both the full analysis set and the safety set contained 20 patients (Table 10-2).

Table 10-2 Analysis sets (Screened set)

Analysis population	PAN+BTZ+Dex N=21 n (%)
Screened set	21 (100.0)
Full analysis set	20 (95.2)
Safety set	20 (95.2)

Source: Table 14.1-3.1

10.4 Demographics

The median age of the patients was 62.5 years (range: 38 to 83 years) with nine patients ≥ 65 years (Table 10-3). All patients were Caucasian; 11 patients (55.0%) were male and nine patients (45.0%) female. The median body mass index was 24.2 kg/m^2 (range: 20.3 to 36.2 kg/m^2).

Relevant medical history and current medical conditions are provided in Listing 16.2.4-1.2.

Table 10-3 Demographic summary (Full analysis set)

Demographic variable	PAN+BTZ+Dex N=20
Age (years)	
Mean (SD)	64.5 (12.42)
Median (Min, Max)	62.5 (38, 83)
Age category (years)-n (%)	
<65	11 (55.0)
≥ 65	9 (45.0)
Sex-n (%)	
Female	9 (45.0)
Male	11 (55.0)
Race-n (%)	
Caucasian	20 (100.0)
Ethnicity-n (%)	
Other	13 (65.0)
Missing	7 (35.0)
Body mass index (kg/m2)	
n	13
Mean (SD)	25.44 (4.23)
Median (Min, Max)	24.21 (20.29, 36.15)

Source: Table 14.1-4.1

11 Efficacy results

This was a non-interventional study with primary data collection to describe the safety profile of the triple combination in real world use. No efficacy assessments were performed.

12 Safety evaluation

12.1 Extent of exposure

12.1.1 Patient exposure

The median duration of exposure to treatment with PAN+BTZ+Dex was 5.14 weeks (range: 1.14 to 48.71 weeks) (Table 12-1). The majority of patients (60.0%) were treated for a period shorter than eight weeks; one patient was treated for a period longer than 48 weeks (i.e. 48.71 weeks).

Table 12-1 Duration of exposure to study treatment (Safety set)

Duration of exposure (unit)	PAN+BTZ+Dex N=20
Exposure categories-n (%) (weeks)	
< 4	5 (25.0)
4 - <8	7 (35.0)
8 - <16	3 (15.0)
16 - <32	2 (10.0)
32 - <48	2 (10.0)
48 - <64	1 (5.0)
Exposure (weeks)	
Mean (SD)	12.56 (14.98)
Median (Min, Max)	5.14 (1.14, 48.71)

Duration of exposure in weeks = (Last dosing date – First dosing date + 1)/7.
Source: Table 14.3-1.1

The median duration of exposure to treatment with panobinostat was 4.79 weeks (range: 0.57 to 48.71 weeks) (Table 12-2). The majority of patients (60.0%) were treated for a period shorter than eight weeks; one patient was treated for a period longer than 48 weeks (i.e. 48.71 weeks).

Table 12-2 Duration of exposure to panobinostat (Safety set)

Duration of exposure (unit)	PAN N=20
Exposure categories-n (%) (weeks)	
< 4	7 (35.0)
4 - <8	5 (25.0)
8 - <16	3 (15.0)
16 - <32	2 (10.0)
32 - <48	2 (10.0)
48 - <64	1 (5.0)
Exposure (weeks)	
Mean (SD)	12.14 (15.16)
Median (Min, Max)	4.79 (0.57, 48.71)

Duration of exposure in weeks = (Last dosing date – First dosing date + 1)/7.
Source: Table 14.3-1.2

12.2 Compliance

Seventeen patients used and fully completed the compliance card. Two patients had medication errors i.e. omission or improper dose (under dose, overdose, and extra dose) (Table 12-3).

Reasons for change or interruption of treatment are provided in Listing 16.2.5-1.1.

Table 12-3 Compliance card summary (Safety set)

	PAN+BTZ+Dex N=20 n (%)
Number of patients with medication errors i.e. omission or improper dose (under dose, overdose, and extra dose)	2 (10.0)
Number of patients using the compliance card	17 (85.0)
Number of patients who came to visit with the compliance card	17 (85.0)
Number of patients who fully completed the compliance card	17 (85.0)

Source: Table 14.3-2.1

12.3 Adverse events

All patients had at least one AE (Table 12-4). Most patients had an AE in the SOC of blood and lymphatic system disorders (55.0%), followed by AEs in the SOC of general disorders and administration site conditions (40.0%), infections and infestations (40.0%), and gastrointestinal disorders (30.0%).

Fifteen patients (75.0%) had a grade 3/4 AE with seven patients (35.0%) in the SOC of blood and lymphatic system disorders.

Table 12-4 AEs by primary system organ class (Safety set)

Primary system organ class	PAN+BTZ+Dex N=20	
	All grades n (%)	Grade 3/4 n (%)
Any primary system organ class	20 (100)	15 (75.0)
Blood and lymphatic system disorders	11 (55.0)	7 (35.0)
Cardiac disorders	2 (10.0)	1 (5.0)
Gastrointestinal disorders	6 (30.0)	1 (5.0)
General disorders and administration site conditions	8 (40.0)	2 (10.0)
Infections and infestations	8 (40.0)	2 (10.0)
Investigations	5 (25.0)	2 (10.0)
Metabolism and nutrition disorders	3 (15.0)	1 (5.0)
Musculoskeletal and connective tissue disorders	3 (15.0)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (5.0)	1 (5.0)
Nervous system disorders	4 (20.0)	2 (10.0)
Psychiatric disorders	2 (10.0)	0
Renal and urinary disorders	1 (5.0)	1 (5.0)
Respiratory, thoracic and mediastinal disorders	3 (15.0)	1 (5.0)
Vascular disorders	3 (15.0)	1 (5.0)

A patient with multiple AEs within a primary system organ class is counted only once in the total row.
System organ classes are presented in alphabetical order.
MedDRA Version 22.0 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.1

The most frequently occurring AE was thrombocytopenia in nine patients (45.0%) followed by fatigue (5 patients, 25.0%), and anemia and pyrexia (4 patients each, 20.0%) (Table 12-5). All other AEs were in three or fewer patients. Six patients (30.0%) had a grade 3/4 AE of thrombocytopenia and three patients had grade 3/4 anemia. All other grade 3/4 AEs were in one or two patients.

Table 12-5 AEs by preferred term (at least 10% in any group) (Safety set)

Preferred term	PAN+BTZ+Dex N=20	
	All grades n (%)	Grade 3/4 n (%)
Any preferred term	20 (100)	15 (75.0)
Thrombocytopenia	9 (45.0)	6 (30.0)
Fatigue	5 (25.0)	1 (5.0)
Anaemia	4 (20.0)	3 (15.0)
Pyrexia	4 (20.0)	1 (5.0)
Bone pain	3 (15.0)	0
Diarrhoea	3 (15.0)	1 (5.0)
Platelet count decreased	3 (15.0)	2 (10.0)
Hypertension	2 (10.0)	1 (5.0)
Hypokalaemia	2 (10.0)	0
Neuropathy peripheral	2 (10.0)	1 (5.0)
Neutropenia	2 (10.0)	1 (5.0)
Pneumonia	2 (10.0)	1 (5.0)
Respiratory tract infection	2 (10.0)	1 (5.0)

Preferred term are sorted in descending order of frequency.
MedDRA Version 22.0 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.1

12.3.1 Analysis of adverse events

Seven patients had AEs suspected to be related to study drug; AEs of diarrhea and fatigue suspected to be related to study drug were reported in two patients each (Table 12-6). All other related AEs were reported in single patients.

Each of grade 3/4 related AEs of diarrhea, fatigue, atrial fibrillation, and dehydration were reported in single patients.

Table 12-6 Treatment-related AEs by preferred term (Safety set)

Preferred term	PAN+BTZ+Dex N=20	
	All grades n (%)	Grade 3/4 n (%)
Any preferred term	7 (35.0)	2 (10.0)
Diarrhoea	2 (10.0)	1 (5.0)
Fatigue	2 (10.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
Dehydration	1 (5.0)	1 (5.0)
Mucosal dryness	1 (5.0)	0
Nausea	1 (5.0)	0
Thrombocytopenia	1 (5.0)	0
Vomiting	1 (5.0)	0

Preferred terms are sorted in descending order of frequency.
MedDRA Version 22.0 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.2

12.3.2 Listing of adverse events by patient

AEs by patient are displayed in Listing 16.2.7-1.1.

12.4 Deaths and other serious or clinically significant adverse events

12.4.1 Deaths

Three patients (15.0%) died on-treatment due to study indication (Table 14.3.1-1.3). Eight patients died more than 30 days after last study treatment (Listing 14.3.2-1.1).

12.4.2 Serious adverse events

Eight patients had at least one serious adverse event (SAE) of whom six patients had a grade 3/4 SAE (Table 12-7). Two patients had a fatal SAE (septic shock and multi organs failure due to progression of underlying disease not related to study drug), four patients had a grade 4 SAE, and three patients a grade 3 SAE (Listing 16.2.7-1.1). Two grade 4 SAEs (atrial fibrillation, dehydration) in one patient were suspected to be related to study drug. The SAEs are described in detail in Section 14.3.3.

Table 12-7 Serious adverse events, regardless of relationship to study drug, by preferred term (Safety set)

Preferred term	PAN+BTZ+Dex N=20	
	All grades n (%)	Grade 3/4 n (%)
Any preferred term	8 (40.0)	6 (30.0)
Acute kidney injury	1 (5.0)	0
Atrial fibrillation	1 (5.0)	1 (5.0)
Dehydration	1 (5.0)	1 (5.0)
Epistaxis	1 (5.0)	1 (5.0)
Headache	1 (5.0)	1 (5.0)
Multiple organ dysfunction syndrome	1 (5.0)	0
Plasmacytoma	1 (5.0)	1 (5.0)
Pneumonia	1 (5.0)	1 (5.0)
Respiratory tract infection	1 (5.0)	1 (5.0)
Septic shock	1 (5.0)	0
Thrombocytopenia	1 (5.0)	1 (5.0)

Preferred terms are sorted in alphabetical order.
MedDRA Version 22.0 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.5

12.4.3 Adverse events leading to discontinuation

Eight patients (40.0%) had AEs leading to treatment discontinuation; two patients had AEs of pyrexia, while other events (PTs) were reported in single patients (Table 12-8). Seven patients had grade 3/4 AEs leading to discontinuation of treatment.

Table 12-8 Adverse events leading to study drug discontinuation, regardless of study drug relationship, by preferred term (Safety set)

Preferred term	PAN+BTZ+Dex N=20	
	All grades n (%)	Grade 3/4 n (%)
Any preferred term	8 (40.0)	7 (35.0)
Pyrexia	2 (10.0)	1 (5.0)
Acute kidney injury	1 (5.0)	1 (5.0)
Diarrhoea	1 (5.0)	1 (5.0)
Hypertension	1 (5.0)	1 (5.0)
Insomnia	1 (5.0)	0
Neuropathy peripheral	1 (5.0)	1 (5.0)
Pneumonia	1 (5.0)	1 (5.0)
Thrombocytopenia	1 (5.0)	1 (5.0)

Preferred terms are sorted in descending order of frequency.
MedDRA Version 22.0 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.7

12.4.4 Listing of deaths, other serious adverse events and other clinically significant adverse events

All patients who died during the study and two-year follow-up period are listed in Listing 14.3.2-1.1.

Patients who experienced SAEs during the study and two-year follow-up period are listed in Listing 16.2.7-1.1.

Patients who discontinued study treatment due to adverse events are listed in Listing 16.2.7-1.1.

12.4.5 Narratives of deaths, other serious adverse events and certain other clinically significant adverse events

Narratives describing deaths, other serious adverse events and certain other clinically significant adverse events are provided in Section 14.3.3.

12.5 Hematology

Hematology values for each patient are provided in Listing 16.2.8-1.1.

12.6 Vital signs, physical findings and other observations related to safety

12.6.1 Vital signs

Vital sign parameters for each patient are provided in Listing 16.2.9-1.1.

12.6.2 Electrocardiogram

Electrocardiogram parameters for each patient are provided in Listing 16.2.9-1.2. None of the patients with an ECG measured had a QTcF >450 ms.

12.7 Summary of safety results

- The median duration of exposure to treatment with PAN+BTZ+Dex was 5.14 weeks (range: 1.14 to 48.71 weeks). The median duration of exposure to treatment with panobinostat was 4.79 weeks (range: 0.57 to 48.71 weeks).
- Seventeen patients used and fully completed the compliance card. Two patients had medication errors i.e. omission or improper dose (under dose, overdose, and extra dose)
- All patients had at least one AE. Most patients had an AE in the system organ class of blood and lymphatic disorders (55.0%), followed by AEs in the SOC of general disorders and administration site conditions (40.0%), infections and infestations (40.0%), and gastrointestinal disorders (30.0%).
- The most frequently occurring AE was thrombocytopenia in nine patients (45.0%) followed by fatigue (5 patients, 25.0%), and anemia and pyrexia (4 patients each, 20.0%).
- Three patients (15.0%) died on-treatment due to study indication.
- Eight patients had an SAE of whom six patients had a grade 3/4 SAE. Two patients had a fatal SAE of septic shock and multi organs failure due to progression of underlying disease not related to study drug.

13 Discussion and overall conclusions

To further characterize the safety profile of the triplet combination under real-world conditions this post authorization safety study collected data from patients prescribed panobinostat according to the EU prescribing information as part of the EU RMP Post Approval Commitments agreed with CHMP at the time of the EU original authorization . The study was planned as a prospective, multicenter, multi-national non-interventional study based on primary data collection for patients diagnosed with relapsed and/or refractory multiple myeloma.

This study was non-interventional and did not impose a therapy protocol, therapeutic interventions or a visit schedule. At study entry, patients had a new or ongoing panobinostat treatment (in combination with bortezomib and dexamethasone) in accordance with the local (country-specific) panobinostat prescribing information.

A total of approximately 425 patients were planned for this study, however, only 20 patients were treated due to changes in treatment preferences making recruitment of patients challenging and ultimately leading to the early termination of the study. The release from the commitment to conduct this PASS study was agreed with CHMP.

The overall study duration was expected to be six years, allowing all patients an observation period of 48 weeks for the PAN+BTZ+Dex treatment period, and a follow-up period of 24 months for second primary malignancy, survival and record for new antineoplastic treatments. However, the median duration of treatment with PAN+BTZ+Dex was 5.14 weeks

with the majority of patients (60.0%) treated shorter than eight weeks. Only one patient was treated for more than 48 weeks.

As expected, the most frequently occurring AE was thrombocytopenia in nine patients of whom six patients had a grade 3/4 AE. Three patients died on treatment due to study indication and eight patients had an SAE.

Conclusions

- Due to early termination of the study, the number of patients is too low to draw any conclusion.
- No new safety signals were observed.

14 Tables, Figures and Listings referred to but not included in the text

14.1 Demographic data

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Table 14.1-1.1 (Page 1 of 1)
Patient disposition
Screened Set

Disposition Reason	PAN+BTZ+DEX N=21 n (%)
Patients	
Enrolled	21 (100.0)
Patients treated	20 (95.2)
End of treatment	20 (95.2)
Primary reason for end of treatment	
Adverse Event	8 (38.1)
Progressive Disease	9 (42.9)
Subject/Guardian Decision	3 (14.3)
Study evaluation after end of treatment	
Patients no longer being followed for study evaluation	12 (57.1)
Patients continuing to be followed for study evaluation	8 (38.1)
Primary reason for study evaluation completion	
Death	6 (28.6)
Study Terminated By Sponsor	2 (9.5)

- Percentage is based on N
- Patients who have completed treatment duration per protocol may have switched to commercial drug.

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Table 14.1-2.1 (Page 1 of 1)
Protocol deviations
Full Analysis Set

Obs	'	PAN+BTZ+DEX N=xx n (%)
1	There is no data to display	

- A subject with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Subjects may have protocol deviations in more than one protocol deviation category.

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Table 14.1-3.1 (Page 1 of 1)
Analysis sets
Screened Set

Analysis Population	PAN+BTZ+DEX N=21 n (%)
Screened set (SCR)	21 (100)
Full analysis set (FAS)	20 (95.2)
Safety set (SAF)	20 (95.2)

N is the number of patients screened.
Percentages are computed using the number of patients screened as the denominator.

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Table 14.1-4.1 (Page 1 of 3)
Demographics
Full Analysis Set

Demographic Variable	PAN+BTZ+DEX N=20
Age (years)	
n	20
Mean	64.5
SD	12.42
Median	62.5
Minimum	38
Maximum	83
Age category (years)-n (%)	
<= 60	9 (45.0)
> 60	11 (55.0)
< 65	11 (55.0)
>= 65	9 (45.0)
Sex-n (%)	
Female	9 (45.0)
Male	11 (55.0)
Race-n (%)	
Caucasian	20 (100.0)
Black	0
Asian	0
Native American	0
Pacific Islander	0
Other	0

- Percentage is based on N

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Table 14.1-4.1 (Page 2 of 3)
Demographics
Full Analysis Set

Demographic Variable	PAN+BTZ+DEX N=20
Ethnicity-n (%)	
Hispanic/Latino	0
Chinese	0
Indian (Indian subcontinent)	0
Japanese	0
Mixed ethnicity	0
Other	13 (65.0)
Missing	7 (35.0)
Weight (kg)	
n	13
Mean	69.55
SD	11.91
Median	72.00
Minimum	47.5
Maximum	93.7
Height (cm)	
n	13
Mean	165.3
SD	8.26
Median	163.0
Minimum	153
Maximum	181
Body mass index (kg/m2)	
n	13
Mean	25.44

- Percentage is based on N

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Table 14.1-4.1 (Page 3 of 3)
Demographics
Full Analysis Set

Demographic Variable	PAN+BTZ+DEX N=20
Body mass index (kg/m2) (cont.)	
SD	4.23
Median	24.21
Minimum	20.29
Maximum	36.15

- Percentage is based on N

14.2 Efficacy and other non-safety data - Not applicable

14.3 Safety data

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Table 14.3-1.1 (Page 1 of 1)
Duration of exposure to study treatment
Safety Set

Duration of exposure (unit)	PAN+BTZ+DEX N=20
Exposure categories-n (%) (weeks)	
< 4	5 (25.0)
4 - <8	7 (35.0)
8 - <16	3 (15.0)
16 - <32	2 (10.0)
32 - <48	2 (10.0)
48 - <64	1 (5.0)
64 - <80	0
80 - <112	0
112 - <144	0
>= 144	0
Exposure (weeks)	
n	20
Mean	12.56
SD	14.98
Median	5.14
Minimum	1.14
Maximum	48.71

- A patient is counted in only one duration range.
- Duration of exposure in weeks = (Last dosing date - First dosing date + 1)/7

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Table 14.3-1.2 (Page 1 of 1)
Duration of exposure to panobinostat
Safety Set

Duration of exposure (unit)	PAN+BTZ+DEX N=20
Exposure categories-n (%) (weeks)	
< 4	7 (35.0)
4 - <8	5 (25.0)
8 - <16	3 (15.0)
16 - <32	2 (10.0)
32 - <48	2 (10.0)
48 - <64	1 (5.0)
64 - <80	0
80 - <112	0
112 - <144	0
>= 144	0
Exposure (weeks)	
n	20
Mean	12.14
SD	15.16
Median	4.79
Minimum	0.57
Maximum	48.71

- A patient is counted in only one duration range.
- Duration of exposure in weeks = (Last dosing date - First dosing date + 1)/7

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Table 14.3-2.1 (Page 1 of 1)
Compliance card summary
Safety Set

	PAN+BTZ+DEX N=20
Number of patients with medication errors i.e. omission or improper dose (underdose, overdose, and extradose) - n(%)	2 (10.0)
Number of patients using the compliance card - n(%)	17 (85.0)
Number of patients who came to visit with the compliance card - n(%)	17 (85.0)
Number of patients who fully completed the compliance card - n(%)	17 (85.0)

14.3.1 Displays of adverse events

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Table 14.3.1-1.1 (Page 1 of 4)
Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Any primary system organ class		
-Total	20 (100)	15 (75.0)
Blood and lymphatic system disorders		
-Total	11 (55.0)	7 (35.0)
Thrombocytopenia	9 (45.0)	6 (30.0)
Anaemia	4 (20.0)	3 (15.0)
Neutropenia	2 (10.0)	1 (5.0)
Leukocytosis	1 (5.0)	0
Leukopenia	1 (5.0)	0
Pancytopenia	1 (5.0)	1 (5.0)
Cardiac disorders		
-Total	2 (10.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
Tachycardia	1 (5.0)	0
Gastrointestinal disorders		
-Total	6 (30.0)	1 (5.0)
Diarrhoea	3 (15.0)	1 (5.0)
Flatulence	1 (5.0)	0
Nausea	1 (5.0)	0
Vomiting	1 (5.0)	0

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.1 (Page 2 of 4)
Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
General disorders and administration site conditions		
-Total	8 (40.0)	2 (10.0)
Fatigue	5 (25.0)	1 (5.0)
Pyrexia	4 (20.0)	1 (5.0)
Mucosal dryness	1 (5.0)	0
Multiple organ dysfunction syndrome	1 (5.0)	0
Infections and infestations		
-Total	8 (40.0)	2 (10.0)
Pneumonia	2 (10.0)	1 (5.0)
Respiratory tract infection	2 (10.0)	1 (5.0)
Bronchitis	1 (5.0)	0
Influenza	1 (5.0)	0
Nasopharyngitis	1 (5.0)	0
Septic shock	1 (5.0)	0
Investigations		
-Total	5 (25.0)	2 (10.0)
Platelet count decreased	3 (15.0)	2 (10.0)
Blood creatinine increased	1 (5.0)	0
Weight decreased	1 (5.0)	0
Metabolism and nutrition disorders		
-Total	3 (15.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.1 (Page 3 of 4)
Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Metabolism and nutrition disorders		
Hypokalaemia	2 (10.0)	0
Dehydration	1 (5.0)	1 (5.0)
Musculoskeletal and connective tissue disorders		
-Total	3 (15.0)	0
Bone pain	3 (15.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
-Total	1 (5.0)	1 (5.0)
Plasmacytoma	1 (5.0)	1 (5.0)
Nervous system disorders		
-Total	4 (20.0)	2 (10.0)
Neuropathy peripheral	2 (10.0)	1 (5.0)
Headache	1 (5.0)	1 (5.0)
Polyneuropathy	1 (5.0)	0
Sciatica	1 (5.0)	0
Psychiatric disorders		
-Total	2 (10.0)	0
Insomnia	1 (5.0)	0
Sleep disorder	1 (5.0)	0

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.1 (Page 4 of 4)
Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Renal and urinary disorders		
-Total	1 (5.0)	1 (5.0)
Acute kidney injury	1 (5.0)	1 (5.0)
Respiratory, thoracic and mediastinal disorders		
-Total	3 (15.0)	1 (5.0)
Epistaxis	1 (5.0)	1 (5.0)
Haemoptysis	1 (5.0)	0
Rhinorrhoea	1 (5.0)	0
Vascular disorders		
-Total	3 (15.0)	1 (5.0)
Hypertension	2 (10.0)	1 (5.0)
Hypotension	1 (5.0)	0

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.2 (Page 1 of 2)
Adverse events, suspected to be study drug related, by primary system organ class, preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Any primary system organ class		
-Total	7 (35.0)	2 (10.0)
Blood and lymphatic system disorders		
-Total	1 (5.0)	0
Thrombocytopenia	1 (5.0)	0
Cardiac disorders		
-Total	1 (5.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
Gastrointestinal disorders		
-Total	4 (20.0)	1 (5.0)
Diarrhoea	2 (10.0)	1 (5.0)
Nausea	1 (5.0)	0
Vomiting	1 (5.0)	0
General disorders and administration site conditions		
-Total	2 (10.0)	1 (5.0)
Fatigue	2 (10.0)	1 (5.0)
Mucosal dryness	1 (5.0)	0
Metabolism and nutrition disorders		
-Total	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.2 (Page 2 of 2)
Adverse events, suspected to be study drug related, by primary system organ class, preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Metabolism and nutrition disorders		
Dehydration	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.3 (Page 1 of 1)
On treatment deaths
Safety Set

Principal cause of death	PAN+BTZ+DEX N=20 n(%)
Total number of deaths	3 (15.0)
Principal cause of death	
Study indication	3 (15.0)
Other	0

- Percentages are computed based on the number of patients in the SAF.
- Primary reason for death comes from death CRF page.

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Table 14.3.1-1.4 (Page 1 of 1)
All deaths on study
Safety Set

Principal cause of death	PAN+BTZ+DEX N=20 n(%)
Total number of deaths	11 (55.0)
Principal cause of death	
Study indication	10 (50.0)
Other	1 (5.0)

- Percentages are computed based on the number of patients in the SAF.
- Primary reason for death comes from death CRF page.

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Table 14.3.1-1.5 (Page 1 of 2)
Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Any primary system organ class		
-Total	8 (40.0)	6 (30.0)
Blood and lymphatic system disorders		
-Total	1 (5.0)	1 (5.0)
Thrombocytopenia	1 (5.0)	1 (5.0)
Cardiac disorders		
-Total	1 (5.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
General disorders and administration site conditions		
-Total	1 (5.0)	0
Multiple organ dysfunction syndrome	1 (5.0)	0
Infections and infestations		
-Total	3 (15.0)	2 (10.0)
Pneumonia	1 (5.0)	1 (5.0)
Respiratory tract infection	1 (5.0)	1 (5.0)
Septic shock	1 (5.0)	0
Metabolism and nutrition disorders		
-Total	1 (5.0)	1 (5.0)
Dehydration	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.5 (Page 2 of 2)
Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
-Total	1 (5.0)	1 (5.0)
Plasmacytoma	1 (5.0)	1 (5.0)
Nervous system disorders		
-Total	1 (5.0)	1 (5.0)
Headache	1 (5.0)	1 (5.0)
Renal and urinary disorders		
-Total	1 (5.0)	0
Acute kidney injury	1 (5.0)	0
Respiratory, thoracic and mediastinal disorders		
-Total	1 (5.0)	1 (5.0)
Epistaxis	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.6 (Page 1 of 1)
Serious adverse events, suspected to be study drug related, by primary system organ class, preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	PAN+BTZ+DEX N=20 Grade 3/4 n (%)
-Any primary system organ class		
-Total	1 (5.0)	1 (5.0)
Cardiac disorders		
-Total	1 (5.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
Metabolism and nutrition disorders		
-Total	1 (5.0)	1 (5.0)
Dehydration	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.7 (Page 1 of 2)
Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	PAN+BTZ+DEX N=20 Grade 3/4 n (%)
-Any primary system organ class		
-Total	8 (40.0)	7 (35.0)
Blood and lymphatic system disorders		
-Total	1 (5.0)	1 (5.0)
Thrombocytopenia	1 (5.0)	1 (5.0)
Gastrointestinal disorders		
-Total	1 (5.0)	1 (5.0)
Diarrhoea	1 (5.0)	1 (5.0)
General disorders and administration site conditions		
-Total	2 (10.0)	1 (5.0)
Pyrexia	2 (10.0)	1 (5.0)
Infections and infestations		
-Total	1 (5.0)	1 (5.0)
Pneumonia	1 (5.0)	1 (5.0)
Nervous system disorders		
-Total	1 (5.0)	1 (5.0)
Neuropathy peripheral	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.7 (Page 2 of 2)
Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Psychiatric disorders		
-Total	1 (5.0)	0
Insomnia	1 (5.0)	0
Renal and urinary disorders		
-Total	1 (5.0)	1 (5.0)
Acute kidney injury	1 (5.0)	1 (5.0)
Vascular disorders		
-Total	1 (5.0)	1 (5.0)
Hypertension	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.8 (Page 1 of 1)
Adverse events requiring dose adjustment or study drug interruption, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Any primary system organ class		
-Total	6 (30.0)	3 (15.0)
Blood and lymphatic system disorders		
-Total	1 (5.0)	1 (5.0)
Thrombocytopenia	1 (5.0)	1 (5.0)
Gastrointestinal disorders		
-Total	2 (10.0)	0
Diarrhoea	1 (5.0)	0
Flatulence	1 (5.0)	0
Infections and infestations		
-Total	2 (10.0)	1 (5.0)
Nasopharyngitis	1 (5.0)	0
Respiratory tract infection	1 (5.0)	1 (5.0)
Nervous system disorders		
-Total	2 (10.0)	1 (5.0)
Headache	1 (5.0)	1 (5.0)
Neuropathy peripheral	1 (5.0)	0

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.9 (Page 1 of 3)
Adverse events requiring significant additional therapy, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Any primary system organ class		
-Total	12 (60.0)	6 (30.0)
Blood and lymphatic system disorders		
-Total	4 (20.0)	3 (15.0)
Thrombocytopenia	3 (15.0)	2 (10.0)
Anaemia	2 (10.0)	2 (10.0)
Leukopenia	1 (5.0)	0
Gastrointestinal disorders		
-Total	2 (10.0)	1 (5.0)
Diarrhoea	1 (5.0)	1 (5.0)
Nausea	1 (5.0)	0
General disorders and administration site conditions		
-Total	1 (5.0)	0
Pyrexia	1 (5.0)	0
Infections and infestations		
-Total	5 (25.0)	1 (5.0)
Pneumonia	2 (10.0)	1 (5.0)
Bronchitis	1 (5.0)	0
Influenza	1 (5.0)	0

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.9 (Page 2 of 3)
Adverse events requiring significant additional therapy, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Infections and infestations		
Respiratory tract infection	1 (5.0)	0
Metabolism and nutrition disorders		
-Total	1 (5.0)	0
Hypokalaemia	1 (5.0)	0
Musculoskeletal and connective tissue disorders		
-Total	1 (5.0)	0
Bone pain	1 (5.0)	0
Nervous system disorders		
-Total	1 (5.0)	0
Neuropathy peripheral	1 (5.0)	0
Renal and urinary disorders		
-Total	1 (5.0)	1 (5.0)
Acute kidney injury	1 (5.0)	1 (5.0)
Respiratory, thoracic and mediastinal disorders		
-Total	1 (5.0)	1 (5.0)
Epistaxis	1 (5.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.9 (Page 3 of 3)
Adverse events requiring significant additional therapy, regardless of study drug relationship, by primary system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
Vascular disorders		
-Total	2 (10.0)	1 (5.0)
Hypertension	2 (10.0)	1 (5.0)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of 'all grades' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

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Table 14.3.1-1.10 (Page 1 of 3)
Adverse events of special interest regardless of study drug relationship by primary system organ class, preferred term
Safety Set

Grouping Preferred term	PAN+BTZ+DEX N=20 All grades n	(%)	Grade 3/4 n	(%)
Any adverse event of special interest -Total	17	(85.0)	11	(55.0)
Carcinogenicity/Second primary malignancy -Total	1	(5.0)	1	(5.0)
Plasmacytoma	1	(5.0)	1	(5.0)
QTc prolongation -Total	1	(5.0)	0	
Multiple organ dysfunction syndrome	1	(5.0)	0	
Renal dysfunction -Total	2	(10.0)	1	(5.0)
Acute kidney injury	1	(5.0)	1	(5.0)
Blood creatinine increased	1	(5.0)	0	
Severe diarrhea -Total	3	(15.0)	1	(5.0)
Diarrhoea	3	(15.0)	1	(5.0)
Severe haemorrhage and thrombocytopenia - thrombocytopenia				

- Groupings are presented alphabetically; preferred terms are sorted within group by descending frequency
- An AE can appear in more than 1 AE group
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a grouping is counted only once in the total row
- The groupings consist of adverse events for which there is a specific clinical interest in connection with PAN or adverse events which are similar in nature.
- Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

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Table 14.3.1-1.10 (Page 2 of 3)
Adverse events of special interest regardless of study drug relationship by primary system organ class, preferred term
Safety Set

Grouping Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Total	11 (55.0)	8 (40.0)
Thrombocytopenia	9 (45.0)	6 (30.0)
Platelet count decreased	3 (15.0)	2 (10.0)
Severe hemorrhage and thrombocytopenia - hemorrhage		
-Total	2 (10.0)	1 (5.0)
Epistaxis	1 (5.0)	1 (5.0)
Haemoptysis	1 (5.0)	0
Severe infections - leukopenia		
-Total	3 (15.0)	1 (5.0)
Neutropenia	2 (10.0)	1 (5.0)
Leukopenia	1 (5.0)	0
Severe infections - pneumonia		
-Total	2 (10.0)	1 (5.0)
Pneumonia	2 (10.0)	1 (5.0)
Severe infections - sepsis		
-Total	1 (5.0)	0
Septic shock	1 (5.0)	0
Tachyarrhythmias		

- Groupings are presented alphabetically; preferred terms are sorted within group by descending frequency
- An AE can appear in more than 1 AE group
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a grouping is counted only once in the total row
- The groupings consist of adverse events for which there is a specific clinical interest in connection with PAN or adverse events which are similar in nature.
- Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

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Table 14.3.1-1.10 (Page 3 of 3)
Adverse events of special interest regardless of study drug relationship by primary system organ class, preferred term
Safety Set

Grouping Preferred term	PAN+BTZ+DEX N=20 All grades n (%)	 Grade 3/4 n (%)
-Total	2 (10.0)	1 (5.0)
Atrial fibrillation	1 (5.0)	1 (5.0)
Tachycardia	1 (5.0)	0

- Groupings are presented alphabetically; preferred terms are sorted within group by descending frequency
- An AE can appear in more than 1 AE group
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple adverse events within a grouping is counted only once in the total row
- The groupings consist of adverse events for which there is a specific clinical interest in connection with PAN or adverse events which are similar in nature.
- Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

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Table 14.3.1-2.1 (Page 1 of 3)
Deaths and serious adverse events in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Total number of subjects affected	
Subjects affected by serious adverse events / exposed (%)	8 / 20 (40.0)
Number of deaths (all causes)	11
Number of deaths resulting from adverse events*	0
Blood and lymphatic system disorders	
Thrombocytopenia	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 0
Cardiac disorders	
Atrial fibrillation	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	1 / 1
Deaths causally related to treatment / all	0 / 0
General disorders and administration site conditions	
Multiple organ dysfunction syndrome	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 1

MedDRA version 22.0
*number of deaths resulting from adverse events corresponds to deaths resulting from serious AE causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurences regardless of causality to treatment
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment

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Table 14.3.1-2.1 (Page 2 of 3)
Deaths and serious adverse events in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Infections and infestations	
Pneumonia	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 0
Respiratory tract infection	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 0
Septic shock	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 1
Metabolism and nutrition disorders	
Dehydration	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	1 / 1
Deaths causally related to treatment / all	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Plasmacytoma	
Subjects affected / exposed (%)	1 / 20 (5.0)

MedDRA version 22.0
*number of deaths resulting from adverse events corresponds to deaths resulting from serious AE causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurences regardless of causality to treatment
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment

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Table 14.3.1-2.1 (Page 3 of 3)
Deaths and serious adverse events in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Plasmacytoma	
Occurrences causally related to treatment / all	0 / 2
Deaths causally related to treatment / all	0 / 0
Nervous system disorders	
Headache	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 0
Renal and urinary disorders	
Acute kidney injury	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 1
Deaths causally related to treatment / all	0 / 0
Respiratory, thoracic and mediastinal disorders	
Epistaxis	
Subjects affected / exposed (%)	1 / 20 (5.0)
Occurrences causally related to treatment / all	0 / 2
Deaths causally related to treatment / all	0 / 0

MedDRA version 22.0
*number of deaths resulting from adverse events corresponds to deaths resulting from serious AE causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurences regardless of causality to treatment
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment

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Table 14.3.1-2.2 (Page 1 of 3)
Non-serious adverse events (threshold >= 10 %) in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Total number of subjects affected	
Subjects affected / exposed (%)	16 / 20 (80.0)
Blood and lymphatic system disorders	
Anaemia	
Subjects affected / exposed (%)	4 / 20 (20.0)
Occurrences (all)	4
Neutropenia	
Subjects affected / exposed (%)	2 / 20 (10.0)
Occurrences (all)	2
Thrombocytopenia	
Subjects affected / exposed (%)	8 / 20 (40.0)
Occurrences (all)	9
Gastrointestinal disorders	
Diarrhoea	
Subjects affected / exposed (%)	3 / 20 (15.0)
Occurrences (all)	3
General disorders and administration site conditions	
Fatigue	
Subjects affected / exposed (%)	5 / 20 (25.0)
Occurrences (all)	7
Pyrexia	
Subjects affected / exposed (%)	4 / 20 (20.0)
Occurrences (all)	6

MedDRA version 22.0
Total number of subjects affected by non-serious AE are those subjects who had at least one PT that met the threshold criteria
Preferred terms with a frequency equal or greater than 10%.

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Table 14.3.1-2.2 (Page 2 of 3)
Non-serious adverse events (threshold >= 10 %) in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Infections and infestations	
Respiratory tract infection	
Subjects affected / exposed (%)	2 / 20 (10.0)
Occurrences (all)	3
Investigations	
Platelet count decreased	
Subjects affected / exposed (%)	3 / 20 (15.0)
Occurrences (all)	4
Metabolism and nutrition disorders	
Hypokalaemia	
Subjects affected / exposed (%)	2 / 20 (10.0)
Occurrences (all)	2
Musculoskeletal and connective tissue disorders	
Bone pain	
Subjects affected / exposed (%)	3 / 20 (15.0)
Occurrences (all)	4
Nervous system disorders	
Neuropathy peripheral	
Subjects affected / exposed (%)	2 / 20 (10.0)
Occurrences (all)	2

MedDRA version 22.0
Total number of subjects affected by non-serious AE are those subjects who had at least one PT that met the threshold criteria
Preferred terms with a frequency equal or greater than 10%.

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Table 14.3.1-2.2 (Page 3 of 3)
Non-serious adverse events (threshold >= 10 %) in overall treatment period by system organ class and preferred term
Safety Set

Primary system organ class Preferred term	PAN+BTZ+DEX N=20
Vascular disorders	
Hypertension	
Subjects affected / exposed (%)	2 / 20 (10.0)
Occurrences (all)	2

MedDRA version 22.0
Total number of subjects affected by non-serious AE are those subjects who had at least one PT that met the threshold criteria
Preferred terms with a frequency equal or greater than 10%.

14.3.2 Listings of deaths, other serious and significant adverse events

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Listing 14.3.2-1.1 (Page 1 of 2)
All deaths
Safety Set

Country/ Subject identifier	Age/ Sex/ Race	Date of last dose/ Study day	Date of death/ Study day	Number of days since last dose	Principal cause of death
[redacted]				27	STUDY INDICATION
				5	STUDY INDICATION
				34	STUDY INDICATION
				14	STUDY INDICATION
				134	STUDY INDICATION
				131	STUDY INDICATION
				200	STUDY INDICATION
				35	STUDY INDICATION
				46	OTHER
				394	STUDY INDICATION

* More than 30 days after last study treatment.
MedDRA version 22.0.

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Listing 14.3.2-1.1 (Page 2 of 2)
All deaths
Safety Set

Country/ Subject identifier	Age/ Sex/ Race	Date of last dose/ Study day	Date of death/ Study day	Number of days since last dose	Principal cause of death
[redacted]				276	STUDY INDICATION

* More than 30 days after last study treatment.
MedDRA version 22.0.

14.3.3 Narratives of deaths, other serious and significant adverse events

Events described in narratives

Patient narratives are provided in accordance with ICH Guideline E3 on Structure and Content of Clinical Study Reports, which requests brief patient narratives for each death, other serious adverse event (SAE), and other significant adverse events judged to be of special interest because of clinical importance.

For this study, narratives are provided for:

- Deaths other than disease progression occurring on study treatment or within 30 days of treatment discontinuation
- SAEs occurring during study treatment or within 30 days of treatment discontinuation
- Treatment discontinuation due to adverse event (AE)
- Adverse events of special interest (AESI) occurring on study treatment or within 30 days of treatment discontinuation
  - Venous thromboembolism
  - Tachyarrhythmias (of grade ≥3)
  - Sepsis (of grade ≥3)
  - Reactivation of hepatitis B infection
  - Pneumonia (of grade ≥3)
  - Leukopenia (of grade ≥3)
  - Hemorrhage (of grade ≥3)
  - Thrombocytopenia (of grade ≥3)
  - Diarrhea
  - Renal dysfunction (of grade ≥3)
  - QTc prolongation
  - Ischaemic heart disease
  - Ischaemic colitis
  - Hypothyroidism
  - Hepatic dysfunction (of grade ≥3)
  - Carcinogenicity/second primary malignancy
  - Increased toxicity in elderly patients (of age ≥65 years)

Organization and indexing of narratives

One narrative is provided for each patient; for patients with multiple events, the narrative describes all events requiring a narrative. The narratives are arranged according to the type of event in the following order: death, SAE, treatment discontinuation due to AE, and AESI.

For each type of event, patient narratives are arranged by patient number starting with the lowest center and patient number.

The patient number, event type(s), event(s) described in each narrative, ordered by treatment, can be seen in the Table of Contents. The full listings of deaths, other SAEs, and treatment discontinuation due to AEs are available in Section 14.3.2.

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BIW	Twice in a week
CT scan	Computed tomography scan
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
ECG	Electrocardiogram
GGT	Gamma-glutamyl transferase
GvHD	Graft versus host disease
LLN	Lower limit of normal
MRI	Magnetic resonance imaging
QW	Once in a week
RBC	Red blood cell
RR	Reference range
SAE	Serious adverse event
SBP	Systolic blood pressure
TIW	Thrice in a week
ULN	Upper limit of normal
WBC	White blood cell

1 Narratives for deaths

No narratives were identified under this category.

2 Narratives for SAEs

Patient [ ] – SAE ( ), treatment discontinuation due to AE ( ), AESI ( )

[redacted]

Patient [D2408-[redacted]] – SAE ([redacted]), treatment discontinuation due to AE ([redacted]), AESI [redacted]

[redacted]

Patient [D2408-[redacted]] – SAE ([redacted]), treatment discontinuation due to AE ([redacted]), AESI ([redacted])

[redacted]

Patient [[redacted]] – SAE ([redacted]), treatment discontinuation due to AE ([redacted]), AESI ([redacted])

[redacted]

Patient [D2408-[redacted]] – SAE ([redacted]), treatment discontinuation due to AE ([redacted])

[redacted]

Patient [[redacted]] – SAE ([redacted]), AESI ([redacted])

[redacted]

[redacted]

Patient [D2408-[redacted]] – SAE ([redacted]), treatment discontinuation due to AE ([redacted]), *AESI* ([redacted])

[redacted]

Patient [D2408-[redacted]] – SAE ([redacted]), AESI ([redacted])

[redacted]

3 Narratives for treatment discontinuation due to AE

Patient [[redacted]] – Treatment discontinuation due to AE ([redacted]), AESI ([redacted])

[redacted]

[redacted]

Patient [D2408-[redacted]] – Treatment discontinuation due to AE ([redacted]), AESI ([redacted])

[redacted]

4 Narrative for Adverse events of special interest:

Patient [D2408-[redacted]] – AESI ([redacted])

[redacted]

Patient [[redacted]] – AESI ([redacted])

[redacted]

[redacted]

Patient [D2408-[redacted]] – AESI ([redacted])

[redacted]

Patient [[redacted]] – AESI ([redacted])

[redacted]

[redacted]

Patient [D2408-[redacted]] – AESI ([redacted])

[redacted]

[redacted]

Patient [D2408-[redacted]] – AESI (*[redacted]*)

[redacted]

Patient [D2408-[redacted]] – AESI (*[redacted]*)

[redacted]

[redacted]

Patient [D2408-[redacted]] – AESI ([redacted])

[redacted]

[redacted]