

Clinical Development

CLBH589 (panobinostat)

**CLBH589D2222: Additional analyses
(FDA PMR-2 BB)**

Statistical Analysis Plan

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1 Introduction

This document is used to prepare unplanned analyses to support the FDA Briefing Book to negotiate the PMR-2 discussions.

1.1 Analysis population and database

LBH589D2222

The analysis set definitions and the database to be used follow the specifications given in CLBH589D2222_SC_SAP_Amendment 1_clean version dated 24-May-2018.

LBH589D2308

The analysis set definitions and the database to be used followed the specifications given in CLBH589D2308 RAP_Module_3_Amendment_5 (clean version) dated 28-Nov-2013.

1.2 Endpoints

LBH589D2222

All endpoints are described in the Interim Analysis SAP for study D2222 (dated 24-May-2018) and in the Clinical Study Protocol unless specified otherwise.

LBH589D2308

Using the original submission database cut-off date Sept 10, 2013, based on the derived response assessments using modified EBMT criteria, ORR will be derived according to IMWG criteria up to the end of cycle 8 (C8D1 -1) for patients still on treatment and up to 168 days from randomization for patients who discontinued. Assessments done after the start of new therapy and withdrawal of consent will not be included in the ORR derivation.

2 List of outputs

2.1 List of tables and figures

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3 Shells

3.1 Tables

Table PMR2-1.1 Clinical notable adverse events by treatment group (Safety set)

Subgroup: xxxx

Safety topic	PAN 20 mg TIW		PAN 20 mg BIW		PAN 10 mg TIW	
	N=xxx		N=xxx		N=xxx	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
QTcF prolongation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
myelosuppression	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
severe hemorrhage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
severe infections (including sepsis/pneumonia)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
severe diarrhea	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
hepatic dysfunction	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
tachyarrhythmias	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ischemic heart disease	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
fatigue/asthenia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
cardiac failure	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
renal dysfunction	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

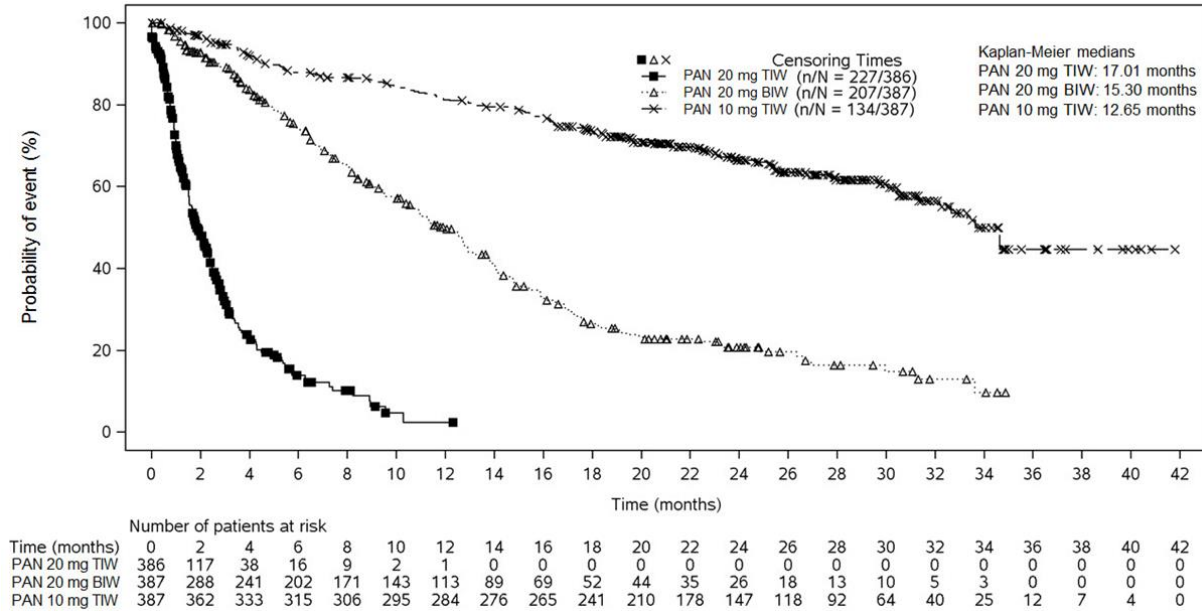
Numbers (n) represent counts of subjects.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version <xx.x>, CTCAE version 4.0.3, Case Retrieval Strategy version <CASVers>.

Programming instructions: Use Table shell 14.3.1.-19 from SAP. Selection and grouping of AEs is based on CRS using flag “Other”. Please use respective “Safety topic” names as presented in the CRS.

Figure PMR2-1 Kaplan-Meier plot of progression-free survival as per IRC assessment (Full analysis set)



Programming Note:

Please display 95% CI for Kaplan-Meier medians for each treatment arm. Use IMWG1 analysis dataset.

This output corresponds to Figure 14.2-2 of the main SAP

Table PMR2-2 Kaplan-Meier estimates of progression-free survival as per IRC assessment (Full analysis set)

	PAN 20 mg BIW N=xxx n (%)	PAN 20 mg TIW N=xxx n (%)	PAN 10 mg BIW N=xxx n (%)
Number of subjects			
With PFS event	xx (xx.x)	xx (xx.x)	xx (xx.x)
With censoring	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kaplan-Meier estimates (95% CI)			
6 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
9 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
12 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Programming Note:

Please display 95% CI for Kaplan-Meier medians for each treatment arm. Use IMWG1 analysis dataset.

This output corresponds to Figure PMR2-2 above

Table ADDON 1-4 Best overall response as per IMWG criteria up to cycle 8 by treatment group (Full analysis set)

	PAN+BTZ+Dex N=xx	PBO+BTZ+Dex N=xx	p-value [2]
Best overall response - n(%)			
Stringent complete response (sCR)	xx (xx.x)	xx (xx.x)	
Complete response (CR)	xx (xx.x)	xx (xx.x)	
Very good partial response (VGPR)	xx (xx.x)	xx (xx.x)	
Partial response (PR)	xx (xx.x)	xx (xx.x)	
Overall Response Rate (ORR)- n(%) (sCR/CR/VGPR or PR)	xx (xx.x)	xx (xx.x)	
95% CI for ORR [1]	[xx.x, xx.x]	[xx.x, xx.x]	x.xx
sCR/CR/VGPR rate - n(%)	xx (xx.x)	xx (xx.x)	
95% CI for sCR/CR/VGPR rate [1]	[xx.x, xx.x]	[xx.x, xx.x]	x.xx

[1] The 95% CI for the rate is computed using the Clopper-Pearson method

[2] p-value, 2-sided, is generated by Cochran-Mantel-Haenszel test

CI - confidence interval