

ICH M11 Digital Clinical Protocol

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> ICH M11 Rapporteur October 23, 2024



FDA Disclaimer

The views and opinions presented here represent my views should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.







Guideline is a high-level document that:

- Provides the background on why a harmonized clinical protocol template is needed, and
- Describes design principles on how the template & technical specification were developed.

Template

 Includes identification of headers, common text, instructions, data fields and terminologies.

Technical Specification

- Serves as a technical representation of the ICH M11 protocol template to support the exchange of protocol information.
- Basis of requirements for a M11 protocol data model.



Project PRISM and M11 Use Case

Sponsors

Bayer, Boehringer Ingelheim, EMD Serono, Bristol Myers Squibb, Takeda

Principal Investigators

RCA principal investigators include CBER, CDER and ODT.



What is it?

A research collaboration and proof of concept project utilizing FDA's production regulatory cloud platform, precisionFDA (pFDA)

Who started it?

Proposed to FDA by industry companies

RELEASE THIS SUMMARY PAGE TO THE PUBLIC. TITLE OF RCA: Project PRISM (PrecisionFDA Regulatory Information Service Module) Center for Biologics Evaluation and Research (CBER FDA Compo Center for Drug Evaluation and Research (CDER); Office Digital Transformation (ODT) FDA Principal Investigat CRER Virginia Hussong, Mark Gray, Ronald Fitzmartin CDER ODT: Chao (Ethan) Chen, Jesse Anderson Collaborat Baver AG and Boehringer Ingelheim International GmbH Collaborator Principal Investigato Vada Perkins TERM OF RCA Three (3) years from the Effective Date ABSTRACT OF THE RESEARCH PLANegulatory and scientific review, as well as submission validation utilizing FDA's production egulatory cloud platform, known as PrecisionFDA. The project will utilize actual regulatory iata suitable for submission to the FDA, as well as third-party tools that FDA currently uses, i.e or eCTD (electronic Common Technical Document) and study data review / validation. However, no submissions or activities involved in this plan take the place of an official ion and/or review proces

ractical, real-wold use cases will test the essential functions of collaborative review, receipt and active or information against current solutions, utilizing mover legalatory and scientific obi and technologies that will enable enhanced sponsor health authority interactions. Exchange at use of large ubunktions, will be enhanced a challenge that continues to grow. The abilithorators are expected to gain important foundational insights into clouds based regulatory or scientific solutions and processes that can improve the thorisonice review and ease of manuaciations for human drug and biologics applications to FDA.

Results, findings and recommendations will be published after each phase, and can be utilized by external stakeholders and global regulatory health authorities to leverage regulatory and scientific platforms and processes that achieve greater efficiencies on a regional and international scale.



PRISM M11 Use Case – Phase 1

• Demonstrate sponsor-to-regulator electronic exchange of a M11compliant protocol and conduct interactive communication



• Results will inform the ICH M11 EWG of any content and / or technical issues prior to reaching ICH Step 3 and 4

PRISM M11 Interactive Communication Spaces on pFDA

FDA

9 Review	FDA - BMS M11 PRISM Interactive Communication Interactive Communication Space for FDA and BMS	683	Active
9 Review	FDA - Takeda M22 PRISM Interactive Communication Interactive communication space for FDA and Takeda	681	Active
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9 Review	FDA - Bayer M11 PRISM Interactive Communication Interactive communication space for FDA and Bayer	677	Active

FDA - Bayer M11 PRISM Interactive Communication

DAaaS

Spaces

Back Home

precision**FDA**

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PRISM

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		Virginia Hussong		Yang Veronica Pei								
		Username:	virginia.hussong	Username:	yangveronica.pei							
		Role:	contributor	Role:	contributor							
		Organization:	virginia.hussong	Organization:	yangveronicapei							
		Joined On:	06/11/2024	Joined On:	06/11/2024							



PRISM M11 Use Case Process Steps



Sponsors create M11 clinical protocols GenerateSponsorstwo human-preparereadable &meetingmachine-packagereadableformats

Sponsors upload meeting pkg to pFDA Private Space

SponsorsFDAIntercopy pkgcopiesBilatoSponsor pkgsCommuFDA-Sponsorto FDAsharedprivate Space

Interactive Bilateral Communication



PRISM M11 Demonstration Use Case Outcomes



3. Gain knowledge

2. Exchange of protocols

Using both **human and machine- readable** formats: DOCX, PDF, and JSON, FHIR

1. Preparation of M11 compliant protocols

Early Stage and Late-Stage Protocols



4. Evaluation of PrecisionFDA

And potential for FDA-Sponsor interactive communication in the cloud

5. Inform FDA

On future uses of a datadriven protocol.



Collaboration Delivers the Digital Protocol









Imagine the future state where...



...the protocol is driven by a common data model that enables limitless personalized views of the protocol.

...For now, all we have is this

		· docuBridg	e [CBER-Production]
Home Review			
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	DRUG:	Zavegepant (BHV-3500)	We use tools
	STUDY NUMBER(S):	BHV3500-301	that load a PDF
	PROTOCOL TITLE:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV- 3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine	of the protocol
	IND NUMBER:	134,120	into a submission
	SPONSOR:		review tool.
	ORIGINAL PROTOCOL DATE:	03-Feb-2020	
	VERSION NUMBER:	v 4.0	
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Prot_CTgov_migraine.pdf - Adobe Acrobat Pro (32-bit)

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С	BHV3500-301 Clinical Protocol, Version 4.0	Confidential
	Phase III double-blind efficacy study zavegepant	Page 5 of 78
Q.	STUDY SUMMARY (SYNOPSIS)	
	Title: BHV3500-301: Phase 3: Double-Blind, Randomized, Placeb Safety and Efficacy Trial of BHV-3500 (zavegepant) Intrana the Acute Treatment of Migraine	
	Rationale: Zavegepant is being developed for the acute treatment of migraine Effectiveness against migraine was demonstrated in BHV35	
	powered, pivotal, Phase 2/3, double-blind, randomized, plac dose-ranging study of zavegepant 5 mg, 10 mg, and 20 mg v	ebo-controlled,
	(IN) administration. The data from this study will allow characterization of the re	hyperlinking
	and efficacy of IN zavegepant versus placebo in the acute tre moderate or severe migraine measuring freedom from pain a	eatment of
	from most bothersome system (nausea, photophobia or phon reported just prior to treatment of the migraine. Information time to onset of action, the duration of action, and the sustain freedom in subjects with migraine will also be obtained.	
•	Target The study will recruit male and female subjects 18 years of a with at least a 1-year history of migraine (with or without au with a diagnosis according to the International Classification Disorders 3 rd edition ¹ , including an age of onset prior to 50, attacks that last about 4-72 hours, not more than 8 attacks of	ra), consistent 1 of Headache migraine moderate or
	severe intensity per month within the last 3 months and not 1 attacks per month.	Forced into a
	Number of Subjects: Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects (approximately 700 per treatm	ent group).
	Subjects will be randomized in a 1:1 ratio to the zavegepant treatment groups. Randomization will be stratified by proph migraine medication use (yes or no).	or placebo
	Primary Objective: To compare the efficacy of zavegepant with placebo in the a of migraine, as measured by co-primary endpoints of pain fr hours postdose, and freedom from the most bothersome sym associated with migraine at 2 hours postdose.	eedom at 2
	Secondary Objectives: 1. To compare zavegepant with placebo for pain relief at 2 postdose.	hours
	2. To compare zavegepant with placebo for return to norma hours postdose according to the Functional Disability sca	
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M11 will break the "document-centric" protocol paradigm

M11 will Enable the Digital Clinical Protocol

Term (Variable)	1.1 Pro	tocol Synopsis	· · · ·			1				
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			rando		and Estin	mands as needed.		User Guidance		In this section, describe the study intervention being tested and any control
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ouler sections			to lai	Relationship content from ToC	Study Ob	ojectives, Endpoints, and Estimands				and Section 6.5, Preparation, Handling, Storage, and Accountability should
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Source: M11 Technical Specification, ICH Step 2a/2b version

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12 My Tasks

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PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND **EFFICACY TRIAL OF BHV-3500** (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE

Overall	Docign
Overall	Design

Intervention Model:	[Parallel]	Population Type:	[Adult Participants]
Control Type:	(Placebo]	Population Diagnosis or Condition:	[Migraine]
Control Description:	[NA]	Population Age:	Minimum: 18 years Maximum: 80 years
Intervention Assignment Method:	[Stratified Randomization]	Site Distribution and Geographic Scope:	[Multicentre] [Multiple Countries]
Adaptive Trial Design:	[No]	Master Protocol Design:	[No]
Drug/Device Combination Product Indicator:	[No]		

[2]				
[Triple]				
[Participant] [Investigator] [Care Provider]				
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[No]				
	[Participant] [Investigator] [Care Provider] [1400] / [1750] [45] [days]			



E My Views

Description

2 ZAVEGEPANT IND

lation	(<the 18<br="" and="" female="" male="" recruit="" study="" subjects="" will="">years of age and older with at least a 1-year history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders 3rd edition1, including an age of onset prior to 50, migraine attacks that last about 4.72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month. >)</the>					
tment	(<zavegepant (in)<br="" 10="" intranasal="" mg="" via="">administration>)</zavegepant>					
point	(< Pain freedom at 2 hours postdose will be assessed using the percentage of subjects with a pain intensity of none at 2 hours postdose. Pain intensity will be measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe), >)					
ulation-Level Summary	(< Treatments compared using a Cochran-Mantel Haensael test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant-placebo) stratified by prophylactic migraine medication use at randomization (yes or no)>)					
current Event	(Strategy)					
ue Medication	(<(The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all endpoints listed below,					

M11 will Enable the Digital Clinical Protocol

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User Guidance	I The protocol	synopsis is a short summary of	the key points of the trial		S	afety \	/iews	
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		subjects per treatment grou		and Section 6.5, Preparation, Handling, Storage, and Acc		 studies). Other reportable 	Header	
		randomized to treatment o		differentiate between each product.		such as cardiovascular a	Definition	
		are presented with time pro	Conformance	Required / Required		malfunctions), laborator	User Guidance	This section describes safety assessments and procedures in this section. Level 3
		to landscape orientation, if	Cardinality	Required / Required		Include the following for		headings can be added as needed.
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other sections			from <u>ToC</u>	Study Intervention and Concomitant Therapy		to report the AESI.		laboratory or other safety assessments (for example, Sponsor or
			representing the			 If it is a measura 		external Independent Data Monitoring Committee).
			protocol hierarchy			done.		
			Relationship			If it is a clinical event, s		Include guidelines for the management of relevant laboratory or other
			(reference to high		Conformance	Required / Required		safety assessment abnormalities.
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M11 Technical Specification, Step 2a/2b version

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PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND EFFICACY TRIAL OF BHV-3500 (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE



Safety Assessments and Procedures

	Procedure	Screening Visit	Baseline Randomization Visit (Day1)	Moderate or Severe Migraine Before Study Drug Administration	Post Study Drug Administration: 15, 30, 45, 60 & 90 minutes 2, 3, 4, 6, 8, 24 & 48 hours	End of Treatment Visit
	Physical Examination	x				X
	Nasal Inspection	x	x			X
;	Vital Signs / Physical Measurements	x	x			x
	Adverse Event and Serious Adverse Event Assessment	x	x	x	x	x
	Sheehan Suicidality Tracking Scale	x	x			
	ECG	x				
	Clinical Safety Laboratory Testing	x				
	Liver Function Tests	x				
	Lipid Panel	x				
	FSH, if Applicable	x				
	Pregnancy Test	x				
	Urinalysis Test	x	x	x		x
	Urine Drug Screen for Drugs of abuse	x				x

Overview of Trial Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Form	Unit Dose Strength	Dosage Level	Route of Administration	Regimen Treatment Period
Experimental	[Active]	[Zavegepant]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]
Placebo Comparator	[Placebo]	[Placebo]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]

Trial Schema



Treatment of migraine must occur within 45 days of randomization (Baseline Visit)

Total study duration is approximately 11 weeks

< Non-serious Adverse Events A non-serious AE is an AE not classified as serious. ·Collection and Reporting of Non-Serious Advers Events The collection of non-serious AE information should begin at the Baseline Visit through the EOT Visit. Non-serious AEs should be followed until conclusion or stabilization, or reported as SA if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment. Laboratory Test Abnormalities

Adverse Events of Special Interest

The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted;
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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🕑 My Tasks

ZAVEGEPANT IND



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PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND **EFFICACY TRIAL OF BHV-3500** (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE

Overall Design



Trial Objectives and Associated Estimands

	Overall	Design		That Objectives at	la Associated Estimatius	Sample Size Determination			
Intervention Model:	[Parallel]	Population Type:	[Adult Participants]	Estimand Characteristic	Description	Sample Size Determination It is anticipated that about 90% of the 700 subjects rand group will have a headache in the allotted time period, r			
Control Type:	[Placebo]	Population [Migrai Diagnosis or Condition:	[Migraine] Population Minimum: 18	Population	- Population	- Population	(<the and="" female<br="" male="" recruit="" study="" will="">subjects 18 years of age and older with at least a 1-year history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache</the>	subjects evaluable for efficacy in each treatment group. The sample size calculation is based on results from the	
Control Description:	[Stratified	Population Age:			Disorders 3rd edition1, including an age of onset prior to 50, migraine attacks that last about 4-72 hours, not more than 8 attacks of moderate or severe intensity per month within	BHV3500-201. A total sample size of 1,260 evaluable sub provide approximately 91% power for the co-primary en hours post dose, approximately 88% power for the co-pr			
Intervention Assignment Method:					the last 3 months and not less than 2 attacks per month. >}	freedom at 2 hours post dose, and approximately 80% p between treatment groups for both endpoints jointly.			
				Treatment	<pre>{<zavegepant (in)="" 10="" <="" intranasal="" mg="" pre="" via=""></zavegepant></pre>				
Adaptive Trial	[No]	Master Protocol	[No]		administration>}	Analvsis Sets Enrolled: Subjects who sign informed consent and are as			
Design:		Design:		Endpoint	{< Pain freedom at 2 hours postdose will be assessed using the percentage of subjects with	number.			
					a pain intensity of none at 2 hours postdose.	Randomized: Subjects in the enrolled analysis set who			
Number of Arms		[2]			Pain intensity will be measured on a 4-point numeric rating scale (O=none, 1=mild,	treatment group assignment (zavegepant or placebo) from			
Trial Blind Schema		[Triple]			2=moderate, 3=severe). >}	 Safety: Subjects in the enrolled analysis set who tak placebo). 			
Number of Participants		[Participant] [Investigator] [Care Provider] [1400] / [1750] [45] [days]		Population-Level Summary	{< Treatments compared using a Cochran- Mantel Haenszel test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant-	 Efficacy: Subjects in the randomized analysis set who: once; (2) have a migraine of moderate or severe intensity a take study drug; and (4) have post-dose efficacy data. 			
					placebo) stratified by prophylactic migraine				
					medication use at randomization (yes or no)>}	Analysis Associated with the Primar			
		1		Intercurrent Event	{Strategy}	Zavegepant will be tested for superiority against place			

Rescue Medication

Overview of Trial Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Form	Unit Dose Strength	Dosage Level	Route of Administration	Regimen Treatment Period
Experimental	[Active]	[Zavegepant]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]
Placebo Comparator	[Placebo]	[Placebo]	[Drug]	[Spray]	[mg]	[10]	[Intranasal]	[45] [days]

{Strategy} {<{The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all endpoints listed below, except the secondary endpoint of rescue medication use within 24 hours postdose}>}

C My Views

🕑 Statistical

ndomized to each treatment l, resulting in approximately 630 p.

he Phase 2/3 dose-ranging study ubjects (630 per group) will endpoint of pain freedom at 2 -primary endpoint of MBS 6 power to detect a difference

signed a subject identification

ho receive a randomized om TWRS.

study drug (zavegepant or

o: (1) are randomized only at the time of dosing (3)

Objective

Zavegepant will be tested for superiority against placebo at an alpha=0.05 level for both co- primary endpoints using the efficacy analysis set. For each endpoint, treatment groups will be compared using a Cochran-Mantel Haenszel test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant - placebo) stratified by prophylactic migraine medication use at randomization (yes or no). The percentage of subjects achieving the endpoint response criteria will be presented with a 95% confidence interval (CI) by treatment 19 group.



PRISM M11 Protocol Use Case - Key Points





Thank You

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