

# ICH M11 Digital Clinical Protocol

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Office of Regulatory Operations

Center for Biologics Evaluation and Research

U.S. Food and Drug Administration

ICH M11 Rapporteur

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# 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.

# ICH M11

## Clinical electronic Structured Harmonised Protocol



- **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

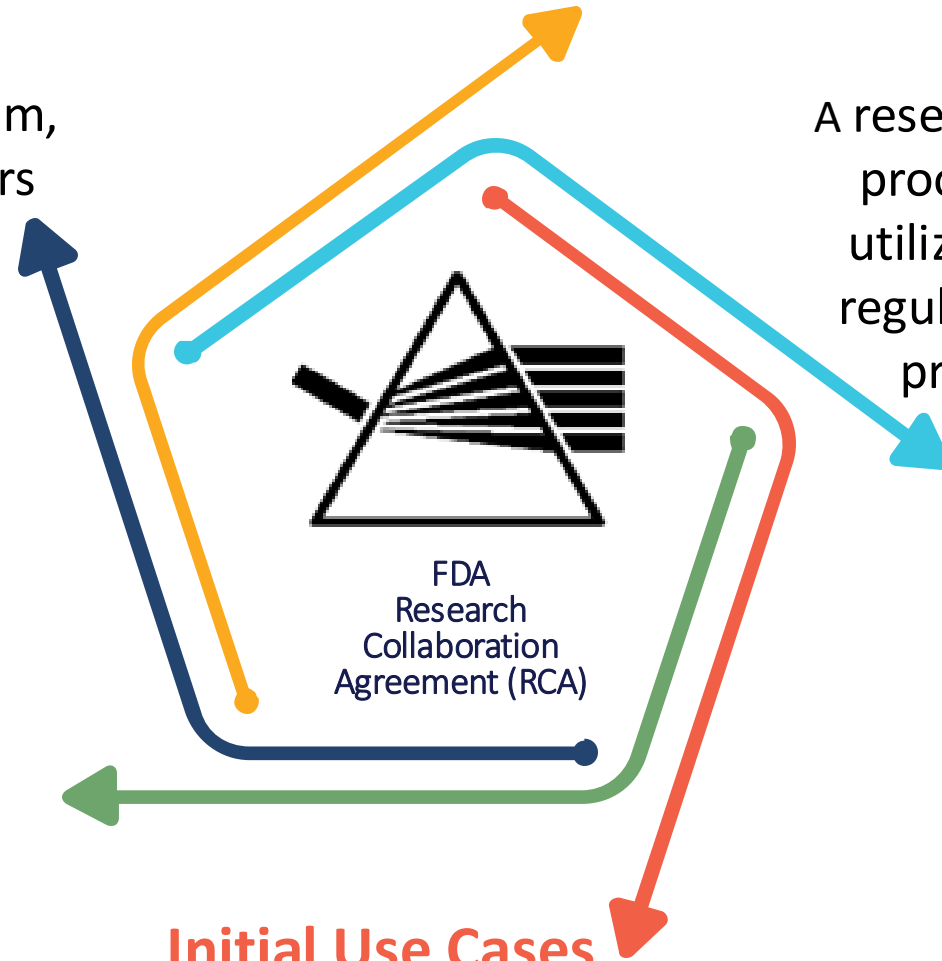


## Sponsors

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

## Principal Investigators

RCA principal investigators include CBER, CDER and ODT.



FDA Research Collaboration Agreement (RCA)

**Initial Use Cases**  
Demonstrate the feasibility of collaborative & interactive review, as well as submission validation.

## 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

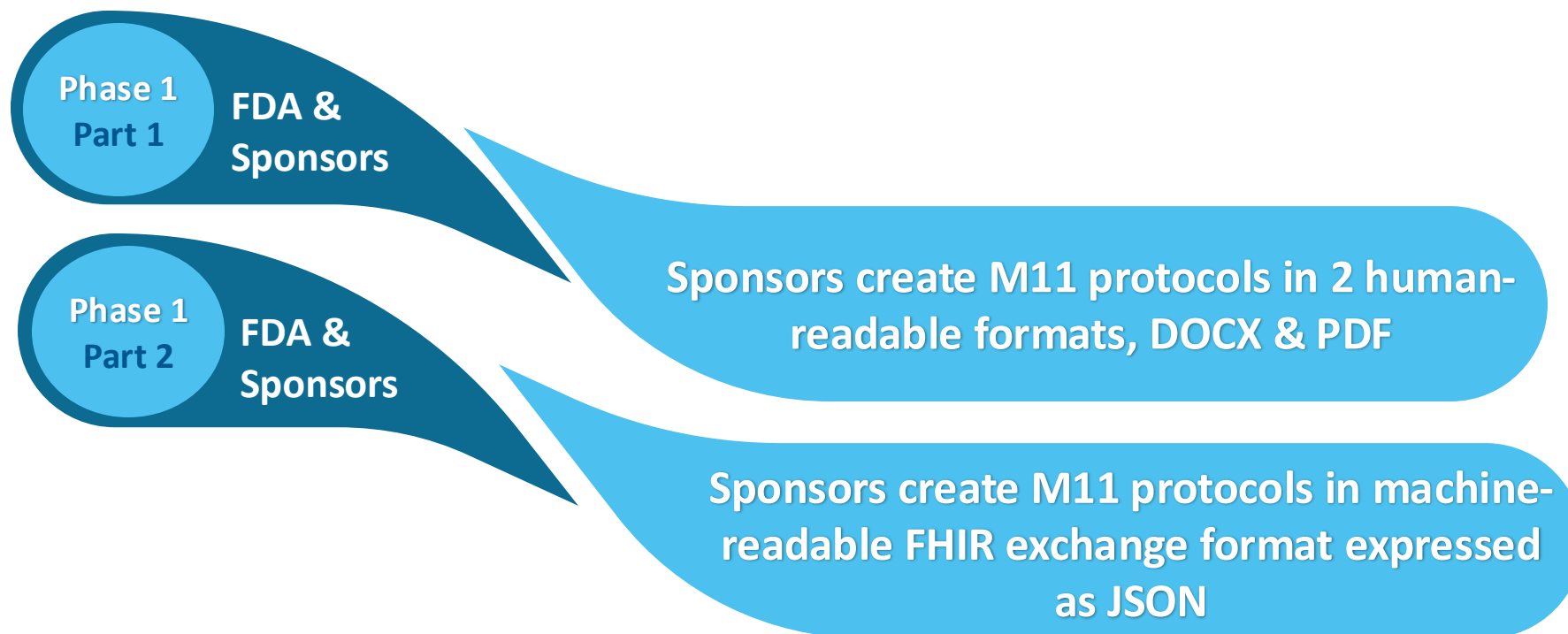
SUMMARY PAGE	
EITHER PARTY MAY, WITHOUT FURTHER CONSULTATION OR PERMISSION, RELEASE THIS SUMMARY PAGE TO THE PUBLIC.	
TITLE OF RCA: Project PRISM (PrecisionFDA Regulatory Information Service Module)	
FDA Component:	Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Office of Digital Transformation (ODT)
FDA Principal Investigators:	Virginia Hussong, Mark Gray, Ronald Fitzmartin
CDER:	Chao (Edhan) Chen, Jesse Anderson
ODT:	Elsae Johanson
Collaborator:	Bayer AG and Boehringer Ingelheim International GmbH
Collaborator Principal Investigator:	Vada Perkins
TERM OF RCA:	Three (3) years from the Effective Date
ABSTRACT OF THE RESEARCH PLAN:	
This research collaboration will demonstrate the feasibility of interactive and collaborative regulatory and scientific review, as well as submission validation utilizing FDA's production regulatory cloud platform, known as PrecisionFDA. The project will utilize actual regulatory data suitable for submission to the FDA, as well as third-party tools that FDA currently uses, i.e., for 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 regulatory submission and/or review process.	
Practical, real-world use cases will test the essential functions of collaborative review, receipt and archive of information against current solutions, utilizing novel regulatory and scientific tools and technologies that will enable enhanced sponsor/health authority interactions. Exchange and use of large submissions will be evaluated, a challenge that continues to grow. The collaborators are expected to gain important foundational insights into cloud-based regulatory and scientific solutions and processes that can improve the submission, review and ease of communications 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 M11-compliant 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



Review	<b>FDA - BMS M11 PRISM Interactive Communication</b> Interactive Communication Space for FDA and BMS	683	Active
Review	<b>FDA - Takeda M22 PRISM Interactive Communication</b> Interactive communication space for FDA and Takeda	681	Active
Review	<b>FDA - Boehringer Ingelheim M11 PRISM Interactive Communication</b> Interactive communication space for FDA and Boehringer Ingelheim	679	Active
Review	<b>FDA - Bayer M11 PRISM Interactive Communication</b> Interactive communication space for FDA and Bayer	677	Active

**Private Area**

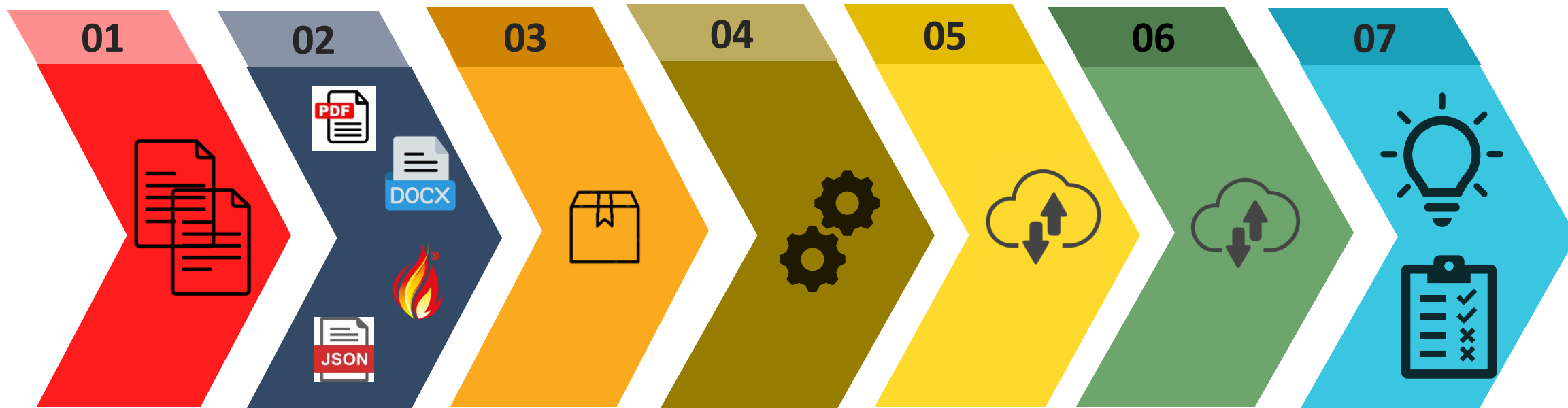
Member	Username	Role	Organization	Joined On
Ron Fitzmartin	ron.fitzmartin	lead	ronfitzmartin	04/22/2024
Virginia Hussong	virginia.hussong	contributor	virginia.hussong	06/11/2024

**Shared Area**

Member	Username	Role	Organization	Joined On
Ron Fitzmartin	ron.fitzmartin	lead	ronfitzmartin	04/22/2024
Walther Seiler	walther.seiler	lead	waltherseiler	04/22/2024
Joanne Petrin	joanne.petrin	contributor	joannepetrin	06/04/2024
Simone Steinbach	simone.steinbach	contributor	simonesteinbach	06/04/2024
Susan Kalisch	susan.kalisch	contributor	susankalisch	06/04/2024
Virginia Hussong	virginia.hussong	contributor	virginia.hussong	06/11/2024
Yang Veronica Pei	yangveronica.pei	contributor	yangveronicapei	06/11/2024



# PRISM M11 Use Case Process Steps



**Sponsors  
create M11  
clinical  
protocols**

**Generate  
two human-  
readable &  
machine-  
readable  
formats**

**Sponsors  
prepare  
meeting  
package**

**Sponsors  
upload  
meeting pkg  
to pFDA  
Private Space**

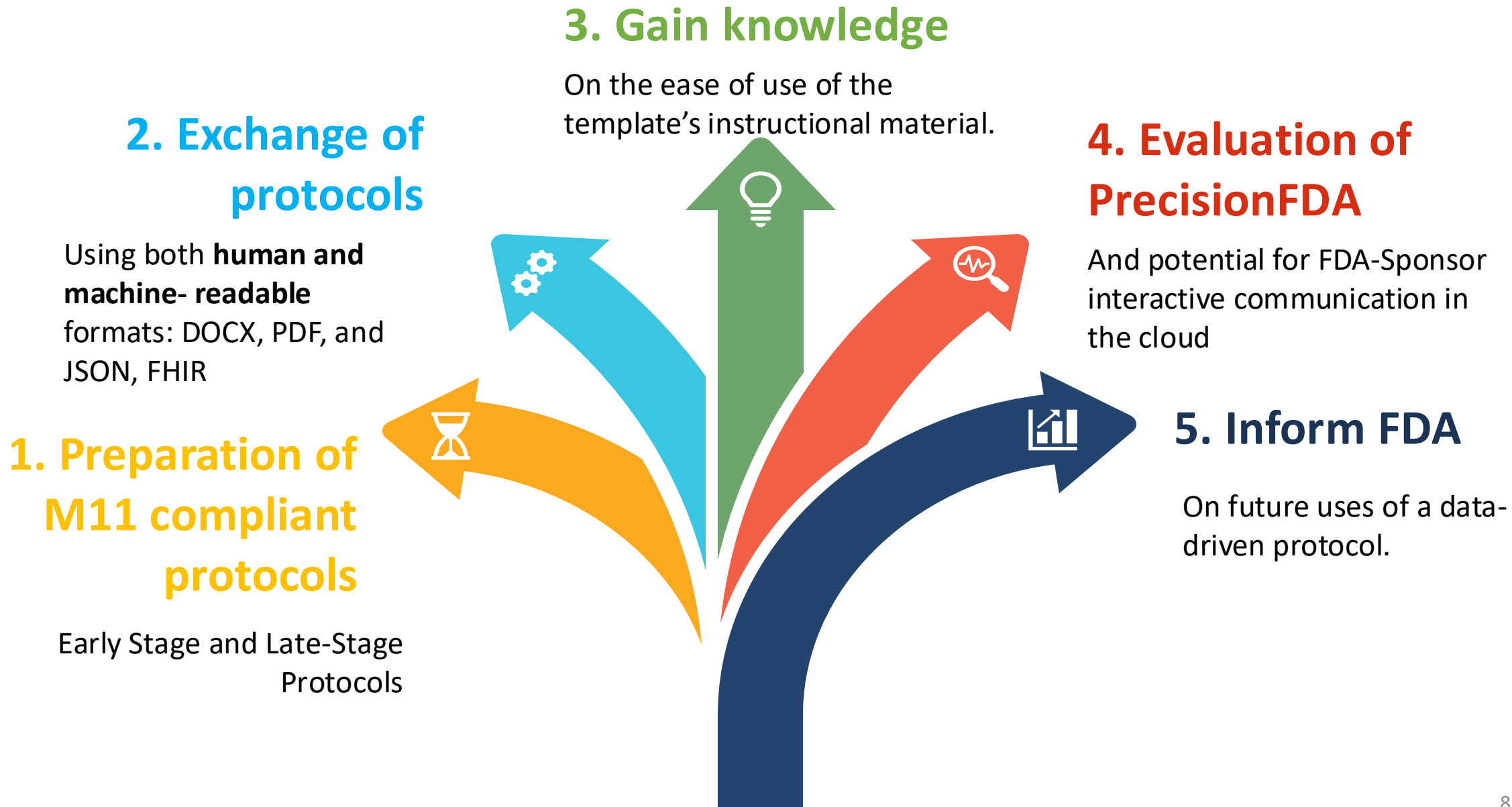
**Sponsors  
copy pkg  
to  
FDA-Sponsor  
shared  
Space**

**FDA  
copies  
Sponsor pkgs  
to FDA  
private Space**

**Interactive  
Bilateral  
Communication**



# PRISM M11 Demonstration Use Case Outcomes







# Collaboration Delivers the Digital Protocol



## M11 CeSHarP



Tech Spec



Template



Guideline



FHIR – Technical Guide (future)



## Unified Study Definition Model (USDM)



USDM



M11/USDM Terminology



USDM JSON API



USDM Conformance Rules



USDMIG



## Utilizing the Digital Protocol – UDP



Use Cases



Implementation Guide(s)



Reference Application

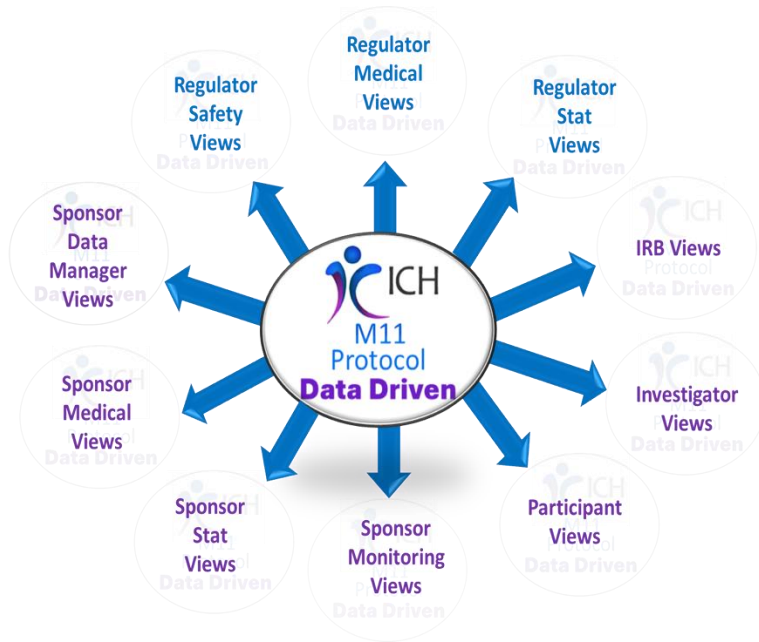


Connectathon



# 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

Home Review

Interact Select Note Highlight Use Hyperlink Setup Edit Duplicate Delete Color Align

Mode Edit Color Align

Source is ClinTrials.gov: [Clintrials.gov](https://www.clintrials.gov) Migraine Protocol

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96

BHV3500-301 Clinical Protocol, Version 4.0 *Confidential*  
 Phase III double-blind efficacy study  
 zavegepant Page 1 of 78

**DRUG:** Zavegepant (BHV-3500)

**STUDY NUMBER(S):** BHV3500-301

**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

**IND NUMBER:** 134,120

**SPONSOR:**

**ORIGINAL PROTOCOL DATE:** 03-Feb-2020

**VERSION NUMBER:** v 4.0

**VERSION DATE:** 02-Jun-2021

We use tools that load a PDF of the protocol into a submission review tool.

## STUDY SUMMARY (SYNOPSIS)

<b>Title:</b>	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
<b>Rationale:</b>	<p>Zavegepant is being developed for the acute treatment of migraine. Effectiveness against migraine was demonstrated in BHV3500-201, a fully powered, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant 5 mg, 10 mg, and 20 mg via intranasal (IN) administration.</p> <p>The data from this study will allow characterization of the relative safety and efficacy of IN zavegepant versus placebo in the acute treatment of moderate or severe migraine measuring freedom from pain and freedom from most bothersome symptom (nausea, photophobia or phonophobia) as reported just prior to treatment of the migraine. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom in subjects with migraine will also be obtained.</p>
<b>Target Population:</b>	The study will recruit male and female 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 Disorders 3 <sup>rd</sup> edition <sup>1</sup> , 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.
<b>Number of Subjects:</b>	Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects (approximately 700 per treatment group). Subjects will be randomized in a 1:1 ratio to the zavegepant or placebo treatment groups. Randomization will be stratified by prophylactic migraine medication use (yes or no).
<b>Primary Objective:</b>	To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.
<b>Secondary Objectives:</b>	<ol style="list-style-type: none"> <li>To compare zavegepant with placebo for pain relief at 2 hours postdose.</li> <li>To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.</li> </ol>

Page by page,  
hyperlinking  
back and forth

Forced into a  
document-  
centric view

**M11 will break the  
“document-centric” protocol paradigm**

# M11 will Enable the Digital Clinical Protocol



Term (Variable)	1.1 Protocol Synopsis
Data Type	Text
Topic, Value or Header	H
Definition	Header
User Guidance	The No t
Conformance	Req
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Prot
Relationship (reference to high level conceptual model)	
Value	1.1
Business rules	Val Rel Con
Duplicate field in other sections	

**Section 1.0**

Term (Variable)	Trial Schema
Data Type	Image
Topic, Value or Header	D
Definition	Visua featu parti scree rand
User Guidance	Key v the t Activ subje rand are p to lat

**Section 1.0**

Term (Variable)	Study Objectives, Endpoints, and Estimands
Data Type	Text
Topic, Value or Header	H
Definition	Heading
User Guidance	In this section, precisely define each clinical question of interest by stating each study objective and specifying the endpoint(s) and estimand(s) that correspond to each study objective. Ensure alignment with every other section of the protocol. Include additional level 2 headers under Section 3 Study Objectives, Endpoints, and Estimands as needed.
Conformance	Required / Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Study Objectives, Endpoints, and Estimands
Relationship (reference to high level conceptual model)	
Value	Study Objectives, Endpoints, and Estimands
Business rules	<b>Value Allowed:</b> Yes <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	

**Section 3.0**

**“Protocol Summary View”**

Term (Variable)	Study Intervention and Concomitant Therapy
Data Type	Text
Topic, Value or Header	H
Definition	Heading
User Guidance	In this section, describe the study intervention being tested and any control product being used. If multiple study interventions are to be evaluated, Section 6.1, Description of Study Intervention, Section 6.3, Dosing and Administration, and Section 6.5, Preparation, Handling, Storage, and Accountability should differentiate between each product.
Conformance	Required / Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Study Intervention and Concomitant Therapy
Relationship (reference to high level conceptual model)	
Value	Study Intervention and Concomitant Therapy
Business rules	<b>Value Allowed:</b> Yes <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	

**Section 6.0**



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

[GSRs](#)
[LORENZ](#)
[CDEROne](#)
[Connect](#)

[My Views](#)
[Overview](#)
[Safety](#)
[Statistical](#)

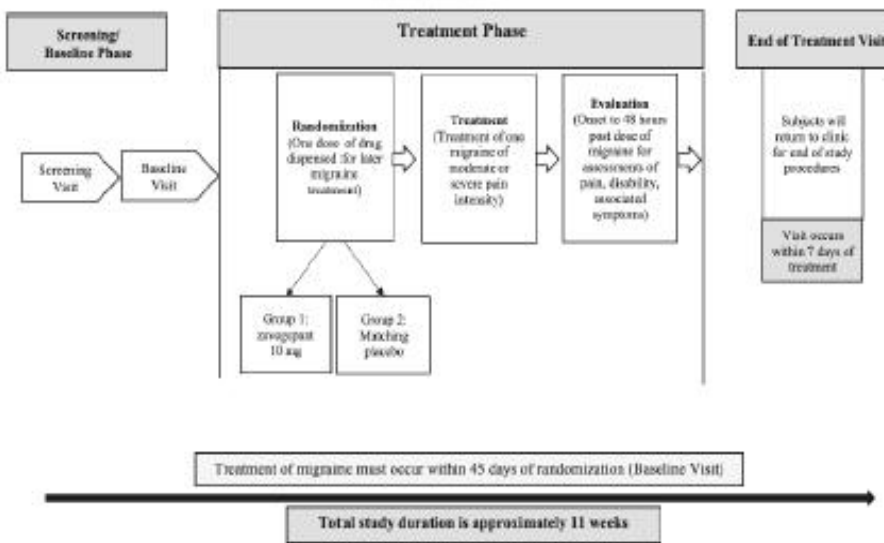
[My Tasks](#)
[Notes](#)
[Discussion](#)
[ZAVEGEPANT IND](#)

**Overall Design**

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

<b>Number of Arms</b>	[2]
<b>Trial Blind Schema</b>	[Triple]
<b>Blinded Roles</b>	[Participant] [Investigator] [Care Provider]
<b>Number of Participants</b>	[1400] / [1750]
<b>Duration</b>	[45] [days]
<b>Independent Committee</b>	[No]

**Trial Schema**



**Trial Objectives and Associated Estimands**

Estimand Characteristic	Description
<b>Population</b>	<The study will recruit male and female 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 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. >
<b>Treatment</b>	<zavegepant 10 mg via intranasal (IN) administration>
<b>Endpoint</b>	< 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). >
<b>Population-Level Summary</b>	< Treatments 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)>
<b>Intercurrent Event</b>	(Strategy)
<b>Rescue Medication</b>	<(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)>

**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]

# M11 will Enable the Digital Clinical Protocol

## “Safety Views”

Term (Variable)	1.1 Protocol Synopsis	<b>Section 1.0</b>
Data Type	Text	
Topic, Value or Header	H	
Definition	Header	
User Guidance	The protocol synopsis is a short summary of the key points of the trial.	

Conformance	Term (Variable)	Trial Schema	<b>Section 1.0</b>
Cardinality	Data Type	Image	
Relationship from ToC representing protocol hierarchy	Topic, Value or Header	D	
Relationship (reference level conceptual model)	Definition	Visual depiction of the trial features of the study design participants through the protocol screening, washout/run-in, randomization, crossover, and other trial features.	
Value	User Guidance	Key visits may also be included in the trial and should correspond to the protocol. Reviewers will evaluate the number of subjects per treatment group randomized to treatment groups are presented with time points to landscape orientation, if applicable.	

Conformance	Term (Variable)	Study Intervention and Concomitant Therapy	<b>Section 6.0</b>
Cardinality	Data Type	Text	
Relationship from ToC representing the protocol hierarchy	Topic, Value or Header	H	
Relationship (reference to high level conceptual model)	Definition	Heading	
Value	User Guidance	In this section, describe the study intervention being tested and the product being used. If multiple study interventions are used, describe each intervention in Section 6.1, Description of Study Intervention, Section 6.3, Dosing and Section 6.5, Preparation, Handling, Storage, and Access. Differentiate between each product.	
Business rules	Conformance	Required / Required	
Duplicate field in other sections	Cardinality		
	Relationship content from ToC representing the protocol hierarchy	Study Intervention and Concomitant Therapy	
	Relationship (reference to high level conceptual model)		
	Value	Study Intervention and Concomitant Therapy	
	Business rules	<b>Value Allowed:</b> Yes <b>Relationship:</b> n/a <b>Concept:</b> n/a	

Conformance	Term (Variable)	Adverse Events of Special Interest	<b>Section 8.0</b>
Cardinality	Data Type	Text	
Relationship from ToC representing the protocol hierarchy	Topic, Value or Header	D	
Relationship (reference to high level conceptual model)	Definition		
Value	User Guidance	Include this section, if applicable. Specify any Adverse Events of Special Interest (e.g., other events that are not reportable to regulatory agencies studies). Other reportable events such as cardiovascular adverse events (malfunctions), laboratory abnormalities, and other events. Include the following for each event: <ul style="list-style-type: none"> <li>The definition of the event to report the AESI.</li> <li>If it is a measurement, include the unit of measurement.</li> <li>If it is a clinical event, specify the time point.</li> </ul>	
Business rules	Conformance	Required / Required	
Duplicate field in other sections	Cardinality		
	Relationship content from ToC representing the protocol hierarchy	Study Assessment and Procedures	
	Relationship (reference to high level conceptual model)		
	Value		
	Business rules	<b>Value Allowed:</b> n/a <b>Relationship:</b> n/a <b>Concept:</b> n/a	

Conformance	Term (Variable)	Safety Assessments and Procedures	<b>Section 8.0</b>
Cardinality	Data Type	Text	
Relationship from ToC representing the protocol hierarchy	Topic, Value or Header	H	
Relationship (reference to high level conceptual model)	Definition		
Value	User Guidance	This section describes safety assessments and procedures in this section. Level 3 headings can be added as needed. <ul style="list-style-type: none"> <li>Identify any non-investigator party responsible for evaluation of laboratory or other safety assessments (for example, Sponsor or external Independent Data Monitoring Committee).</li> <li>Include guidelines for the management of relevant laboratory or other safety assessment abnormalities.</li> </ul>	
Business rules	Conformance	Optional	
Duplicate field in other sections	Cardinality		
	Relationship content from ToC representing the protocol hierarchy	Adverse Events and Serious Adverse Events	
	Relationship (reference to high level conceptual model)		
	Value	Efficacy Assessments and Procedures	
	Business rules	<b>Value Allowed:</b> Yes <b>Relationship:</b> n/a <b>Concept:</b> n/a	



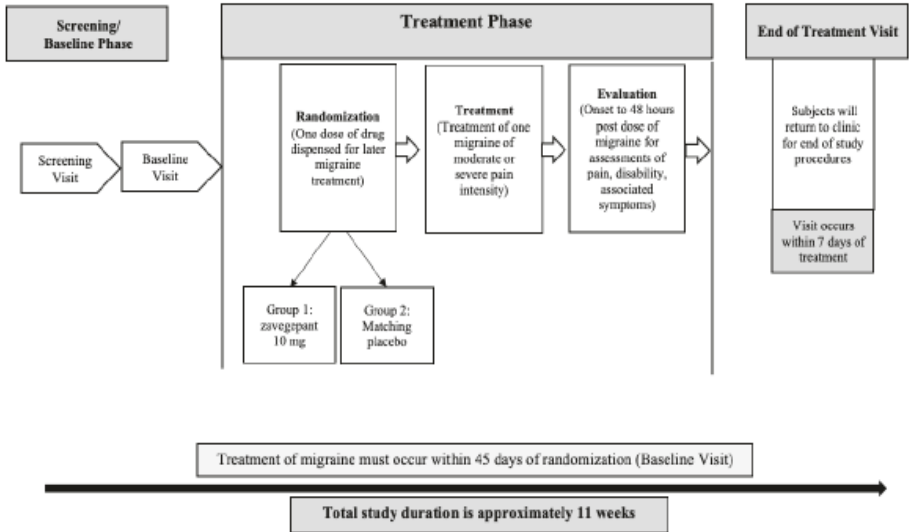
**PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND EFFICACY TRIAL OF BHV-3500 (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE**

Navigation menu with buttons for GSRs, LORENZ, CDEROne, Connect, My Views, Overview, Safety, Statistical, My Tasks, Notes, Discussion, ZAVEGEPANT IND. An arrow points to the 'Safety' button.

**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**



**Adverse Events of Special Interest**

**< Non-serious Adverse Events**  
 A *non-serious AE* is an AE not classified as serious.  
 ·Collection and Reporting of Non-Serious Adverse 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 SAEs 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**  
 The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

**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

# M11 will Enable the Digital Clinical Protocol



## “Statistical View”

Term (Variable)	1.1 Protocol Synopsis
Data Type	Text
Topic, Value or Header	H

### Section 1.0

Term (Variable)	Study Objectives, Endpoints, and Estimands
Data Type	Text
Topic, Value or Header	H

### Section 3.0

Term (Variable)	Study Intervention and Concomitant Therapy
Data Type	Text
Topic, Value or Header	H

### Section 6.0

Term (Variable)	Sample Size Determination
Data Type	Text
Topic, Value or Header	H

### Section 9.0

Term (Variable)	Analysis Supporting Primary Objective(s)
Data Type	Text
Topic, Value or Header	D

### Section 9.0

Term (Variable)	Analysis Sets
Data Type	Text
Topic, Value or Header	D

### Section 9.0

Definition	Detailed description of all efficacy assessments presented in the SoA
User Guidance	Analysis sets to support each analysis will be specified here and described in the Statistical Analysis Plan.
Conformance	Required/Repeated Optional/Repeated
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Analysis Sets
Relationship (reference to high level conceptual model)	
Value	
Business rules	<b>Value Allowed:</b> n/a <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	

Definition	
User Guidance	
Conformance	
Cardinality	
Relationship content from ToC representing the protocol hierarchy	
Relationship (reference to high level conceptual model)	
Value	
Business rules	

User Guidance	
Conformance	Required / Req
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Study Interv
Relationship (reference to high level conceptual model)	
Value	Study Interv
Business rules	<b>Value Allowed:</b> n/a <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	Duplicate field in other sections

User Guidance	In this section, product being 6.1, Description and Section 6.3 differentiate be
Conformance	Required / Req
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Statistic
Relationship (reference to high level conceptual model)	
Value	Sample
Business rules	<b>Value Allowed:</b> n/a <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	

User Guidance	This section size and calculation. If the pl explicitly explorat diseases
Conformance	Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Analysis Supporting P
Relationship (reference to high level conceptual model)	
Value	
Business rules	<b>Value Allowed:</b> n/a <b>Relationship:</b> n/a <b>Concept:</b> n/a
Duplicate field in other sections	

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

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[Safety](#)
[Statistical](#)

[My Tasks](#)
[Notes](#)
[Discussion](#)
[ZAVEGEPANT IND](#)

**Overall Design**

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

<b>Number of Arms</b>	[2]
<b>Trial Blind Schema</b>	[Triple]
<b>Blinded Roles</b>	[Participant] [Investigator] [Care Provider]
<b>Number of Participants</b>	[1400] / [1750]
<b>Duration</b>	[45] [days]

**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 Objectives and Associated Estimands**

Estimand Characteristic	Description
<b>Population</b>	{<The study will recruit male and female 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 Disorders 3rd edition <sup>1</sup> , 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. >}
<b>Treatment</b>	{<zavegepant 10 mg via intranasal (IN) administration>}
<b>Endpoint</b>	{< 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). >}
<b>Population-Level Summary</b>	{< Treatments 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)>}
<b>Intercurrent Event</b>	{(Strategy)}
<b>Rescue Medication</b>	{<(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)>}

**Sample Size Determination**

It is anticipated that about 90% of the 700 subjects randomized to each treatment group will have a headache in the allotted time period, resulting in approximately 630 subjects evaluable for efficacy in each treatment group.

The sample size calculation is based on results from the Phase 2/3 dose-ranging study BHV3500-201. A total sample size of 1,260 evaluable subjects (630 per group) will provide approximately 91% power for the co-primary endpoint of pain freedom at 2 hours post dose, approximately 88% power for the co-primary endpoint of MBS freedom at 2 hours post dose, and approximately 80% power to detect a difference between treatment groups for both endpoints jointly.

**Analysis Sets**

Enrolled: Subjects who sign informed consent and are assigned a subject identification number.

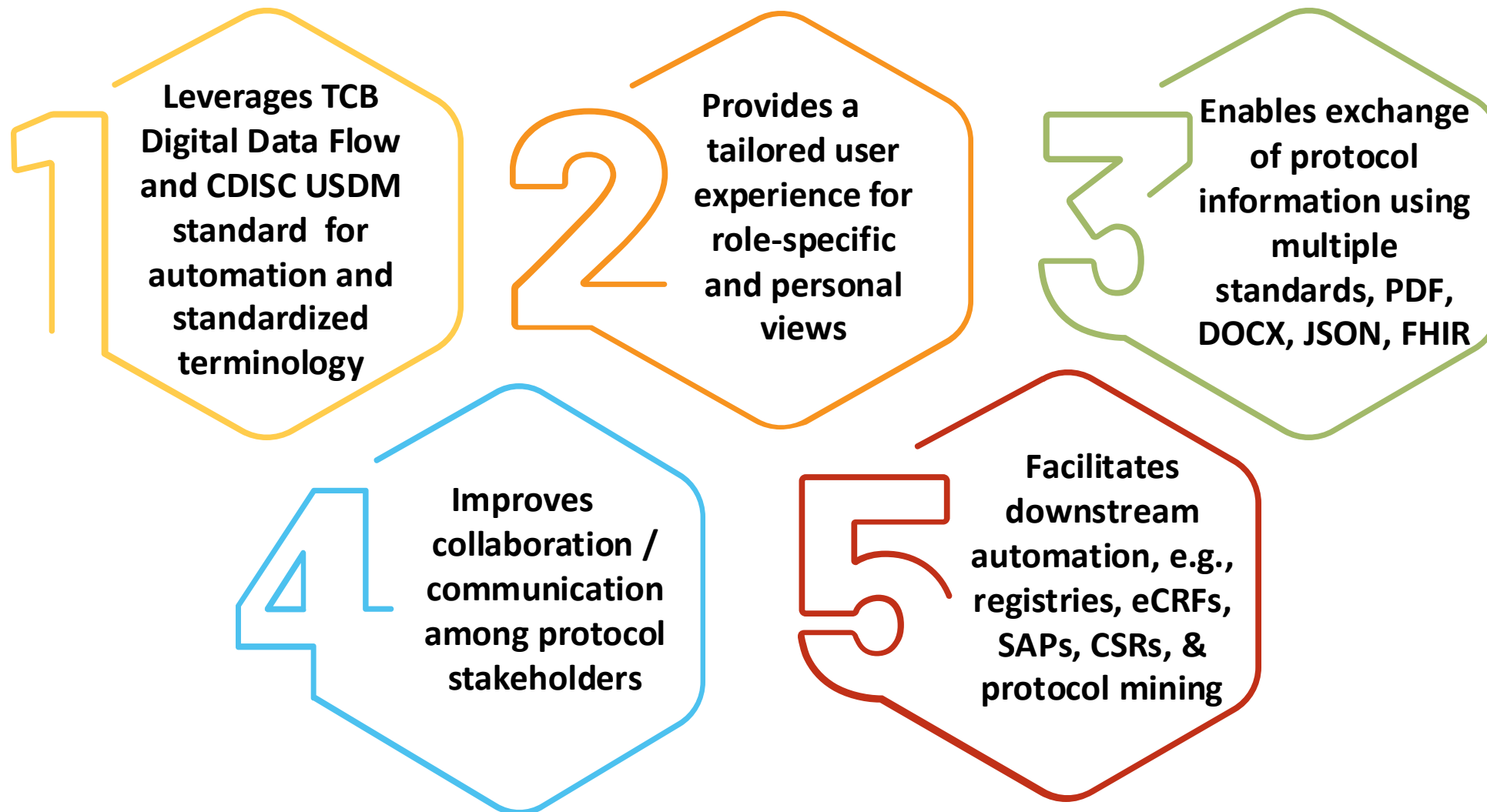
- Randomized:** Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo) from TWRS.
- Safety:** Subjects in the enrolled analysis set who take study drug (zavegepant or placebo).
- Efficacy:** Subjects in the randomized analysis set who: (1) are randomized only once; (2) have a migraine of moderate or severe intensity at the time of dosing (3) take study drug; and (4) have post-dose efficacy data.

**Analysis Associated with the Primary 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 group.



# PRISM M11 Protocol Use Case - Key Points



**Thank You**

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