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REGULATORY SUBMISSION PACKAGE

PRE-IND MEETING MATERIALS

Prepared in accordance with FDA Guidance: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023)

21 CFR Part 312 | Type B Meeting Request

Cromaglutide (OBEGO™)

Internal Code: OBS-2020 | GLP-1 Receptor Agonist | Subcutaneous Injection

Field	Details
Package Contains	Pre-IND Meeting Request Letter; Briefing Document; Meeting Minutes
Meeting Type	Type B — Pre-IND
Requested Meeting Date	November 2017 (exact date TBD per FDA scheduling)
Sponsor	Panacea Therapeutics, Inc.
Regulatory Lead	Aastha Dave, Lead Regulatory Affairs
FDA Division	Division of Metabolism and Endocrinology Products (DMEP), CDER
CFR Reference	21 CFR Part 312
Related IND	IND-2018-PT-0042 (submitted March 2018)

500 BioInnovation Drive, Suite 300, Cambridge, MA 02139
adave@panaceatherapeutics.com | (617) 555-0192

Portfolio Note: All three documents in this package are **RA-authored** deliverables. The Pre-IND Meeting Request Letter and Briefing Document are prepared by RA prior to the meeting. The Meeting Minutes are drafted by RA during the meeting and finalized post-meeting following FDA review and any corrections. The Formal Meetings guidance referenced throughout is: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023 draft guidance).

Contents

DOCUMENT 1 OF 3

Pre-IND Meeting Request Letter

Type B Meeting | 21 CFR Part 312

Document Owner: Regulatory Affairs All content in this document is RA-authored

Date: October 16, 2017

To:
Dr. [Name], Division Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Metabolism and Endocrinology Products (OMEP)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

From:
Aastha Dave, Lead Regulatory Affairs
Panacea Therapeutics, Inc.
500 BioInnovation Drive, Suite 300
Cambridge, MA 02139
adave@panaceatherapeutics.com | (617) 555-0192

Re: Request for Pre-IND (Type B) Meeting — Cromaglutide (OBS-2020 / OBEGO™) | IND Candidate for Chronic Weight Management

Dear Dr. [Name],

Panacea Therapeutics, Inc. (“the Sponsor”) respectfully requests a **Type B Pre-IND Meeting** with the Division of Metabolism and Endocrinology Products (DMEP) to discuss the planned Investigational New Drug (IND) application for **cromaglutide (OBS-2020; OBEGO™)**, a novel, long-acting glucagon-like peptide-1 receptor

agonist (GLP-1 RA) intended for the chronic management of obesity and overweight with comorbidity in adult patients.

This meeting request is submitted in accordance with the FDA guidance *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023 draft guidance). The Sponsor anticipates submitting the IND for cromaglutide in Q1 2018 and seeks FDA input on the proposed first-in-human (FIH) clinical study design, Chemistry, Manufacturing, and Controls (CMC) requirements for the FIH phase, and nonclinical data sufficiency to support Phase 1 entry.

1. Drug and Proposed Indication

Cromaglutide (OBS-2020) is a synthetic 39-amino acid peptide GLP-1 receptor agonist incorporating a proprietary C-18 fatty diacid acylation modification that confers albumin binding and an extended half-life of approximately 168 hours, supporting once-weekly subcutaneous administration. Cromaglutide is proposed for development as an adjunct to a reduced-calorie diet and increased physical activity for **chronic weight management** in:

- Adults with **obesity** (BMI $\geq$30 kg/m^2), or
- Adults with **overweight** (BMI $\geq$27 kg/m^2) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease)

2. Regulatory Background and Rationale for Meeting

Cromaglutide is a New Molecular Entity (NME) with no prior IND, NDA, or foreign marketing authorisation. Panacea Therapeutics intends to submit an initial IND for Phase 1 first-in-human studies in Q1 2018. The Sponsor is requesting this Pre-IND meeting to seek FDA's guidance on key programmatic questions prior to IND submission to ensure alignment on:

1. The adequacy of the nonclinical data package to support FIH entry
2. The proposed Phase 1 SAD/MAD study design (Protocol PT-CROMA-001)
3. CMC requirements for the investigational drug product at the FIH stage
4. The regulatory pathway and any special designations that may be applicable (e.g., Fast Track, Breakthrough Therapy)

3. Meeting Format and Logistics

Parameter	Details
Meeting Type	Type B — Pre-IND
Preferred Format	Teleconference or in-person (Silver Spring, MD); written response also acceptable
Requested Date Range	November 2017 (specific dates provided in Attachment A)
Proposed Duration	60 minutes
Sponsor Attendees	Aastha Dave (Lead, RA); Dr. [CMO Name] (Chief Medical Officer); Dr. [Nonclinical Name] (Head, Nonclinical); Dr. [CMC Name] (Head, CMC)
Briefing Document	To be submitted 30 days prior to the meeting date per FDA guidance

4. Questions for the Meeting

The following questions will be addressed in detail in the accompanying Briefing Document. A summary is provided here to assist FDA in determining appropriate meeting participants and scheduling.

1. **[Nonclinical — Toxicology]:** Is the proposed nonclinical package, comprising 4-week rat and 13-week NHP repeat-dose GLP-compliant toxicology studies, safety pharmacology core battery, and genotoxicity panel, adequate to support initiation of the Phase 1 SAD/MAD study in healthy adults?
2. **[Nonclinical — Carcinogenicity]:** Given that cromaglutide did not induce thyroid C-cell hyperplasia or MTC in a 6-month preliminary carcinogenicity screen, does FDA agree that a Boxed Warning for MTC risk is not warranted in the IB or investigational label at the time of IND submission?
3. **[Clinical — Phase 1 Design]:** Does FDA concur with the proposed Phase 1 SAD/MAD study design (Protocol PT-CROMA-001), including the starting dose of 0.5 mg SC, dose escalation scheme, and subject population (healthy

adults with BMI 27–40 kg/m^2)?

4. **[CMC]:** What level of CMC information is required at IND submission for a synthetic peptide drug product administered in a Phase 1 FIH study? Specifically, does FDA consider the proposed analytical control strategy (identity, assay, purity, bioactivity, sterility, endotoxin) sufficient for the investigational stage?
5. **[Regulatory Pathway]:** Based on the proposed indication and nonclinical profile, would cromaglutide be eligible for **Fast Track Designation** under 21 CFR §312.82? Would FDA consider the available data sufficient to support a **Breakthrough Therapy Designation** request at a later stage?

5. Attachments

Attachm	Description
A	Proposed meeting dates and Sponsor availability
B	Proposed Sponsor attendee list and credentials
C	Summary of cromaglutide nonclinical programme (2 pages)
D	Draft Protocol PT-CROMA-001 synopsis (3 pages)

Panacea Therapeutics appreciates FDA's time and looks forward to a productive dialogue. Please confirm receipt of this request and advise on scheduling at your earliest convenience.

Respectfully submitted,

Aastha Dave
Lead, Regulatory Affairs
Panacea Therapeutics, Inc.
adave@panaceatherapeutics.com | (617) 555-0192

DOCUMENT 2 OF 3

Pre-IND Meeting Briefing Document

Type B Meeting | 21 CFR Part 312 | Submitted 30 Days Prior to Meeting per FDA Formal Meetings Guidance

Document Owner: Regulatory Affairs All content in this document is RA-authored

Field	Details
Sponsor	Panacea Therapeutics, Inc.
Drug Name	Cromaglutide (OBEGO™; OBS-2020)
Meeting Type	Type B — Pre-IND
FDA Division	DMEP, OMEP, CDER
Meeting Date	November 14, 2017 (confirmed)
Document Date	October 14, 2017 (30 days prior)
Regulatory Lead	Aastha Dave, Lead Regulatory Affairs
Document Version	1.0 (Final)

6. Executive Summary

Panacea Therapeutics, Inc. is developing **cromaglutide (OBS-2020; OBEGO™)**, a novel once-weekly subcutaneous GLP-1 receptor agonist, for the chronic management of obesity (BMI $\geq$30 kg/m^2) and overweight with comorbidity (BMI $\geq$27 kg/m^2 with $\geq$1 weight-related comorbidity).

Cromaglutide is a New Molecular Entity (NME) with a differentiated preclinical profile relative to approved GLP-1 RAs, most notably the **absence of thyroid C-cell hyperplasia or medullary thyroid carcinoma (MTC)** in carcinogenicity studies,

and a projected longer duration of weight loss maintenance based on murine model data.

The Sponsor intends to submit a commercial IND for cromaglutide in **Q1 2018**, with initiation of the first-in-human (FIH) Phase 1 SAD/MAD study (**Protocol PT-CROMA-001**) anticipated in Q2 2018. This Briefing Document presents the rationale, supporting data, and five key questions for which the Sponsor seeks FDA input at the Pre-IND meeting.

7. Drug Background

7.1 Pharmacology and Mechanism of Action

Cromaglutide is a synthetic 39-amino acid peptide GLP-1 receptor agonist incorporating a proprietary C-18 fatty diacid moiety conjugated via a bifunctional mini-PEG linker to lysine at position 26. This modification confers reversible, non-covalent albumin binding, dramatically extending the terminal elimination half-life to approximately **168 hours** ($\sim$7 days) and enabling once-weekly subcutaneous dosing.

Cromaglutide produces the following pharmacodynamic effects:

- Glucose-dependent stimulation of pancreatic insulin secretion
- Suppression of postprandial glucagon release
- Delayed gastric emptying, reducing the rate of nutrient absorption
- Direct action on hypothalamic appetite-regulating centres, reducing caloric intake

In vitro receptor characterisation confirms high-potency, selective GLP-1R agonism (EC_{50} = 0.03 nM; $>$1,000-fold selectivity over GIP, glucagon, and related receptors).

7.2 Nonclinical Efficacy

In diet-induced obese (DIO) C57BL/6 mice, once-weekly subcutaneous cromaglutide at 3 mg/kg produced a mean body weight reduction of **21.6%** from baseline over 12 weeks of treatment. Notably, post-cessation weight regain was substantially attenuated compared to a semaglutide reference arm in the same model (28% vs. 58% of lost weight regained at 4 weeks post-treatment; $p<0.01$), supporting the hypothesis of improved weight loss maintenance relative to existing GLP-1 RAs.

7.3 Proposed Clinical Development

Phase	Study	N	Duration	Primary Objective
Phase 1	PT-CROMA-001	80	12 wks	Safety, tolerability, PK/PD
Phase 2	PT-CROMA-101	320	28 wks	Dose selection; preliminary efficacy
Phase 3	CERES-1	1,210	52 wks	Efficacy vs. placebo
Phase 3	CERES-2	1,106	68 wks	Efficacy vs. semaglutide
Phase 3	CERES-3	892	104 wks	Long-term safety
Phase 3	CERES-CARDIO	2,418	3 yrs	Cardiovascular outcomes

8. Nonclinical Data Summary

8.1 Completed Studies Supporting IND Entry

Study	Model	Key Finding
Primary pharmacology	HEK293 GLP-1R cell line	EC_{50} = 0.03 nM; >1,000-fold selectivity
In vivo efficacy	DIO C57BL/6 mouse	21.6% body weight reduction; attenuated post-cessation regain
4-week repeat-dose tox	Sprague-Dawley rat	NOAEL: 30 mg/kg/day SC; reversible GI effects at high doses
13-week repeat-dose tox	Cynomolgus monkey	NOAEL: 10 mg/kg/day; no organ toxicity
Safety pharmacology (CNS)	Rat (Irwin battery)	No adverse effects at 30× projected clinical dose
Safety pharmacology (CV)	hERG assay; anaesthetised dog	No QTc prolongation; no haemodynamic effects
Safety pharmacology (resp.)	Rat plethysmography	No respiratory effects
Genotoxicity (Ames)	*S. typhimurium*; *E. coli*	Negative
Genotoxicity (micronucleus)	Mouse bone marrow	Negative
Preliminary carcinogenicity	hGLP1R transgenic mouse (6 mo)	**No thyroid C-cell hyperplasia; no MTC**

8.2 Planned Nonclinical Studies

The following studies will be initiated concurrently with or following IND submission:

- 26-week rat and 52-week NHP chronic toxicology (GLP-compliant; to support Phase 2 and 3)

- 2-year rat carcinogenicity study (to support NDA)
- Reproductive and developmental toxicology (Segments I–III; to support Phase 3 enrolment of women of child-bearing potential)
- Juvenile animal study (if paediatric indication pursued)

9. Proposed Phase 1 Study Design Synopsis

Protocol: PT-CROMA-001
Title: A Phase 1, Randomised, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose (SAD/MAD) Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Cromaglutide in Healthy Adult Volunteers and Adults with Obesity

Parameter	Details
Phase	1
Design	Randomised, double-blind, placebo-controlled; SAD then MAD cohorts
Population	Healthy adults; BMI 27–40 kg/m^2; ages 18–65
Enrolment	Up to N = 80
Starting Dose (SAD-1)	0.5 mg SC single dose
Dose Escalation	SAD: 0.5, 1.25, 2.5, 5.0 mg; MAD: 2.5, 5.0, 10.0 mg QW $\times$ 4 doses
Safety Oversight	Safety Review Committee (SRC); DSMB; stopping rules for pancreatitis, hypersensitivity
Primary Endpoints	Safety and tolerability; PK profile (AUC, C_{max}, t_{12})
Secondary Endpoints	PD markers (fasting glucose, insulin, glucagon); immunogenicity (ADA testing)
AE Grading	CTCAE v5.0

9.1 Starting Dose Justification

The proposed starting dose of **0.5 mg SC** is derived from the NOAEL of 30 mg/kg/day established in the 4-week Sprague-Dawley rat study. Applying a **1/600 safety factor** to the NOAEL, converted to a human equivalent dose (HED) using standard body surface area scaling (21 CFR Part 312, Appendix D), yields a calculated Maximum Recommended Starting Dose (MRSD) of **0.5 mg**, which the Sponsor considers appropriately conservative for a first-in-human study.

10. CMC Summary for FIH Phase

10.1 Drug Substance

Cromaglutide drug substance is manufactured by Fmoc solid-phase peptide synthesis (SPPS) with solution-phase acylation at the Panacea Therapeutics API Facility in Cambridge, MA (FDA-registered). Current purity specification for FIH use is $\geq$98.0% by RP-HPLC, with individual impurities $\leq$0.5% and total impurities $\leq$1.5%.

10.2 Drug Product

The investigational drug product is formulated as a sterile aqueous solution for subcutaneous injection, filled into single-dose Type I glass pre-filled syringes (0.5 mL per syringe). Three strengths are proposed: 2.5 mg, 5 mg, and 10 mg per syringe. Sterility is ensured by aseptic fill-finish with 100% visual inspection and release testing per USP <71> and USP <788>.

10.3 Proposed IND-Stage Analytical Control Strategy

Test	Method	IND-Stage Specification
Identity	Peptide mapping / MS	Conforms
Assay	RP-HPLC	95.0–105.0% of label claim
Purity	RP-HPLC	Total impurities $\leq$3.0% (NDA stage: $\leq$1.5%)
Bioactivity	GLP-1R cell-based assay	70–130% of reference standard
Sterility	USP <71>	No growth
Endotoxins	LAL / USP <85>	$<$1.0 EU/mL
Particulates	USP <788>	Meets compendial limits

11. Questions for FDA

The Sponsor respectfully requests FDA's written or verbal responses to the following questions. Questions are organized by functional area and listed in order of priority.

Question 1 — Nonclinical: Adequacy of Toxicology Package for FIH Entry

Does FDA agree that the completed nonclinical package — comprising a 4-week GLP-compliant rat study (NOAEL: 30 mg/kg/day), a 13-week GLP-compliant NHP study (NOAEL: 10 mg/kg/day), safety pharmacology core battery (ICH S7A/S7B), and genotoxicity panel (Ames test and micronucleus assay, both negative) — is adequate to support initiation of the proposed Phase 1 SAD/MAD study in healthy adult volunteers at a starting dose of 0.5 mg SC?

Sponsor Position: The Sponsor believes the completed nonclinical studies provide an adequate safety basis for FIH entry. The starting dose of 0.5 mg provides a $>$600-fold safety margin over the rat NOAEL (HED-adjusted) and a $>$200-fold margin over the projected therapeutic dose range (2.5–10 mg QW). The safety phar-

macology package is consistent with ICH S7A/S7B requirements for the relevant organ systems.

Question 2 — Nonclinical: Thyroid C-Cell Findings and Boxed Warning

Given that cromaglutide did not induce thyroid C-cell hyperplasia or medullary thyroid carcinoma (MTC) in a 6-month preliminary carcinogenicity screen in hGLP1R transgenic mice, does FDA agree that a Boxed Warning for thyroid C-cell tumour risk is not warranted in the Investigator's Brochure or investigational label at the time of IND submission? Does FDA recommend any additional nonclinical studies to characterise this finding further before IND submission?

Sponsor Position: The Sponsor acknowledges that the GLP-1 RA class is associated with thyroid C-cell tumour risk in rodents, requiring a Boxed Warning for approved agents (semaglutide, liraglutide). However, the preliminary carcinogenicity data for cromaglutide suggest a potentially differentiated profile. The Sponsor proposes to include a precautionary statement in the IB regarding the GLP-1 RA class effect while noting the absence of a thyroid C-cell signal for cromaglutide specifically, and to await the definitive 2-year rat carcinogenicity data before making a final label determination.

Question 3 — Clinical: Phase 1 SAD/MAD Study Design

Does FDA concur with the proposed Phase 1 SAD/MAD study design (Protocol PT-CROMA-001), including: (a) the proposed starting dose of 0.5 mg SC and dose escalation scheme; (b) the subject population of healthy adults with BMI 27–40 kg/m^2, ages 18–65; and (c) the safety review committee (SRC) structure and stopping rules for adverse events of special interest (pancreatitis, hypersensitivity reactions)?

Sponsor Position: The proposed design reflects standard FIH practice for subcutaneous peptide therapeutics. The BMI-restricted healthy volunteer population ensures the study population is representative of the intended therapeutic population while avoiding the complexity of enrolling patients with active obesity-related comorbidities at the FIH stage.

Question 4 — CMC: Analytical Control Strategy for IND Stage

Does FDA consider the proposed IND-stage analytical control strategy (identity by peptide mapping/MS; assay by RP-HPLC; purity $\leq$3.0%; bioactivity 70–130%; sterility per USP <71>; endotoxins $<$1.0 EU/mL; particulates per USP <788>) sufficient to support Phase 1 investigational use of cromaglutide? The Sponsor plans to tighten specifications progressively through Phase 2 and Phase 3 development.

Sponsor Position: The proposed control strategy is commensurate with the exploratory nature of Phase 1 and is consistent with FDA's published expectations for investigational synthetic peptide drug products. Specifications will be progressively tightened based on manufacturing experience and clinical development stage.

Question 5 — Regulatory Pathway: Special Designations

Based on the proposed indication for chronic weight management in adults with obesity or overweight with comorbidity, and the preliminary nonclinical data indicating a potentially differentiated efficacy and safety profile relative to approved GLP-1 RAs: (a) Would cromaglutide be eligible for **Fast Track Designation** under 21 CFR §312.82? (b) At what stage of clinical development, and based on what data, would FDA consider a **Breakthrough Therapy Designation (BTD)** request appropriate?

Sponsor Position: The Sponsor believes cromaglutide meets the criteria for Fast Track Designation, given the serious nature of the proposed indication and the potential to address unmet medical needs. The Sponsor intends to submit a Fast Track Designation request concurrently with or shortly after IND submission. BTD will be considered following Phase 2 data, subject to demonstration of a substantial improvement over available therapies.

DOCUMENT 3 OF 3

Pre-IND Meeting Minutes

Type B Meeting | November 14, 2017 | Division of Metabolism and Endocrinology Products (DMEP), CDER

Document Owner: Regulatory Affairs Drafted by RA during meeting; finalized post-FDA review

Note: These minutes were drafted by Panacea Therapeutics Regulatory Affairs during the meeting and represent the Sponsor's record of the discussion. Per FDA's Formal Meetings guidance, these minutes were submitted to FDA within 30 days of the meeting for FDA review and correction. FDA's written responses to the five questions are incorporated below as received.

Parameter	Details
Meeting Type	Type B — Pre-IND
Meeting Date	November 14, 2017
Meeting Format	Teleconference
Duration	60 minutes (10:00 – 11:00 AM EST)
FDA Division	DMEP, OMEP, CDER
Minutes Drafted by	Aastha Dave, Lead Regulatory Affairs, Panacea Therapeutics
Minutes Submitted to FDA	December 14, 2017 (30 days post-meeting)
FDA Review Complete	January 8, 2018
Minutes Finalized	January 10, 2018

Attendees

Panacea Therapeutics:

- Aastha Dave — Lead, Regulatory Affairs (Sponsor RA lead; minute-taker)
- Dr. [CMO Name] — Chief Medical Officer
- Dr. [Nonclinical Name] — Head, Nonclinical Research
- Dr. [CMC Name] — Head, CMC

FDA (DMEP, CDER):

- Dr. [FDA Division Director] — Division Director, DMEP (Chair)
- Dr. [FDA Clinical Reviewer] — Clinical Reviewer
- Dr. [FDA Nonclinical Reviewer] — Nonclinical Reviewer
- Dr. [FDA CMC Reviewer] — CMC Reviewer

Background and Meeting Purpose

FDA opened the meeting by confirming receipt and review of the Briefing Document submitted October 14, 2017. The Division Director confirmed that FDA reviewers had prepared written responses to all five questions, which would be provided to the Sponsor following the meeting and incorporated into the official meeting minutes.

12. Meeting Discussion and FDA Responses

12.1 Question 1 — Nonclinical: Adequacy of Toxicology Package

Sponsor Question: Does FDA agree that the completed nonclinical package is adequate to support initiation of the proposed Phase 1 SAD/MAD study at a starting dose of 0.5 mg SC?

FDA Response (Written, January 8, 2018): FDA agrees that the completed nonclinical package, as described in the Briefing Document, is generally adequate to support initiation of a Phase 1 SAD/MAD study in healthy adult volunteers at the proposed starting dose of 0.5 mg SC, provided that: (1) all pivotal studies referenced were conducted under GLP conditions per 21 CFR Part 58; and (2) the complete study reports are included in the IND submission at the time of filing. FDA notes that the proposed safety margins (>600-fold over rat NOAEL) are appropriate. FDA reminds the Sponsor that IND safety reporting requirements per 21 CFR §312.32 will apply upon IND submission.

Discussion Summary: The FDA nonclinical reviewer confirmed that the toxicology package is consistent with ICH M3(R2) guidance for FIH studies. No additional nonclinical studies were recommended prior to IND submission. FDA requested that complete study reports be submitted at the time of IND filing rather than in summary format only.

Action Item (Sponsor): Ensure all pivotal GLP-compliant nonclinical study reports are included in their entirety in the IND submission. RA to confirm with Nonclinical team prior to IND filing.
Owner: Aastha Dave, RA | **Due:** Prior to IND submission (Q1 2018)

12.2 Question 2 — Nonclinical: Thyroid C-Cell Findings and Boxed Warning

Sponsor Question: Does FDA agree that a Boxed Warning for thyroid C-cell tumour risk is not warranted in the IB or investigational label at the time of IND submission?

FDA Response (Written, January 8, 2018): FDA acknowledges the preliminary carcinogenicity data presented for cromaglutide. However, FDA cannot confirm the absence of a Boxed Warning requirement at this time, as the definitive 2-year rat carcinogenicity study has not yet been completed. FDA recommends that the Sponsor include a class-level precautionary statement regarding GLP-1 RA thyroid C-cell tumour risk in the Investigator's Brochure and investigational label pending the results of the completed long-term carcinogenicity studies. FDA will re-evaluate the need for a Boxed Warning upon review of the completed 2-year rat carcinogenicity data, which should be submitted as an IND amendment prior to NDA filing.

Discussion Summary: The FDA nonclinical reviewer explained that the 6-month preliminary screen is not considered sufficient to definitively exclude the risk. The Sponsor agreed to include a class-level precautionary statement in the IB and expressed intent to expedite the 2-year rat carcinogenicity study.

Action Item (Sponsor): (1) Include GLP-1 RA class-level thyroid C-cell precautionary statement in IB v1.0. (2) Expedite initiation of 2-year rat carcinogenicity study. (3) Submit carcinogenicity data as IND amendment when available.
Owner: Nonclinical/Tox (studies); RA (IB and IND amendment)

Due: IB v1.0 prior to IND; carcinogenicity study per timeline

12.3 Question 3 — Clinical: Phase 1 SAD/MAD Study Design

Sponsor Question: Does FDA concur with the proposed Phase 1 SAD/MAD study design, including starting dose, subject population, and SRC structure?

FDA Response (Written, January 8, 2018): FDA has reviewed the Phase 1 study design synopsis and has no major objections to the proposed design. FDA concurs with: (a) the proposed starting dose of 0.5 mg SC based on the submitted MRSD calculation; (b) the proposed healthy volunteer population (BMI 27–40 kg/m^2, ages 18–65) for the FIH study; and (c) the proposed SRC structure and stopping rules for adverse events of special interest. FDA recommends that the final protocol include explicit criteria for dose escalation hold and stopping based on pre-specified safety thresholds for nausea/vomiting (Grade $\geq$3), pancreatitis (any grade), and hypersensitivity reactions (Grade $\geq$2). FDA also recommends inclusion of an adequate wash-out period between SAD and MAD cohorts.

Discussion Summary: The FDA clinical reviewer confirmed general agreement with the design but requested that pre-specified safety stopping criteria be more explicitly defined. The Sponsor agreed to incorporate these recommendations.

Action Item (Sponsor): Revise Protocol PT-CROMA-001 to include explicit, pre-specified dose escalation hold and stopping criteria per FDA recommendation. Ensure adequate SAD-to-MAD wash-out period is specified.
Owner: Clinical Affairs (protocol revision); RA (IND submission review)
Due: Prior to IND submission (Q1 2018)

12.4 Question 4 — CMC: Analytical Control Strategy

Sponsor Question: Does FDA consider the proposed IND-stage analytical control strategy sufficient to support Phase 1 investigational use?

FDA Response (Written, January 8, 2018): FDA considers the proposed IND-stage analytical control strategy generally acceptable for Phase 1 use, with the following comments: (1) FDA recommends that a validated bioactivity

(potency) method be in place prior to first use of the drug product in Phase 1; (2) FDA requests that the purity specification of $\leq$3.0% total impurities be tightened to $\leq$2.0% prior to initiation of Phase 2, with a commitment to achieve $\leq$1.5% by NDA; (3) FDA requests that a drug substance reference standard be established and characterised prior to IND submission.

Discussion Summary: The FDA CMC reviewer raised no concerns about the overall control strategy but provided specific comments on the potency method and purity specification tightening timeline. The Sponsor agreed to all three points.

Action Item (Sponsor): (1) Validate GLP-1R cell-based potency assay prior to Phase 1 initiation. (2) Commit to tightening purity spec to $\leq$2.0% before Phase 2. (3) Establish and characterise drug substance reference standard prior to IND submission.
Owner: CMC team (analytical); RA (IND CMC section)
Due: Reference standard and potency method: prior to IND; purity: prior to Ph 2

12.5 Question 5 — Regulatory Pathway: Special Designations

Sponsor Question: Would cromaglutide be eligible for Fast Track Designation, and when would BTD be appropriate?

FDA Response (Written, January 8, 2018): Regarding Fast Track Designation (FTD): FDA agrees that the proposed indication for chronic weight management in adults with obesity or overweight with comorbidity may qualify for FTD under 21 CFR §312.82, given that obesity is associated with serious and life-threatening comorbidities. FDA encourages the Sponsor to submit a formal FTD request, which may be submitted concurrently with or any time after IND submission. Regarding Breakthrough Therapy Designation (BTD): FDA cannot prejudge eligibility for BTD at this stage. FDA advises the Sponsor to submit a BTD request following completion of Phase 2 studies if the data demonstrate a substantial improvement over available therapies on a clinically meaningful endpoint.

Discussion Summary: FDA confirmed that FTD is a realistic pathway for cromaglutide given the indication. The Sponsor confirmed intent to submit a concurrent FTD

request with the IND.

Action Item (Sponsor): Prepare and submit Fast Track Designation request concurrently with IND submission (Q1 2018). Evaluate BTD request following Phase 2 data readout (anticipated Q4 2020).
Owner: Aastha Dave, RA
Due: FTD: Q1 2018 (concurrent with IND); BTD evaluation: Q4 2020

13. Summary of Action Items

#	Action Item	Owner	Due Date
1	Include complete GLP nonclinical study reports in IND submission	RA / Nonclinical	Prior to IND
2	Add class-level thyroid C-cell precautionary statement to IB v1.0	RA / Nonclinical	Prior to IND
3	Initiate 2-year rat carcinogenicity study; submit results as IND amendment	Nonclinical / RA	Per study timeline
4	Revise Protocol PT-CROMA-001 with explicit stopping criteria and wash-out	Clinical / RA	Prior to IND
5	Validate GLP-1R bioactivity assay prior to Phase 1 initiation	CMC	Prior to Ph 1 start
6	Establish and characterise drug substance reference standard	CMC	Prior to IND
7	Commit purity spec tightening to $\leq$2.0% before Phase 2	CMC	Prior to Ph 2
8	Submit Fast Track Designation request (concurrent with IND)	Aastha Dave, RA	Q1 2018
9	Evaluate BTD request following Phase 2 data readout	Aastha Dave, RA	Q4 2020

Closing

FDA thanked the Sponsor for the well-prepared Briefing Document. Both parties agreed that the Pre-IND meeting was productive and that no major barriers to IND submission have been identified. FDA confirmed that official written responses to all five questions would be transmitted to the Sponsor within 30 days of the meeting date.

Minutes prepared by: Aastha Dave, Lead Regulatory Affairs, Panacea Therapeutics, Inc.
Date of draft: November 15, 2017
Submitted to FDA for review: December 14, 2017
Date finalized (post-FDA review): January 10, 2018