

P-175

Brenipatide, a GIP/GLP-1 Receptor Agonist: Clinical Data Supporting Dose Selection for Substance Use, Psychiatric and Immunologic Disorders

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OBJECTIVE

- To evaluate the safety, PK, and PD across a range of BMI to determine a brenipatide dosing regimen for substance use, psychiatric, and immunologic disorders.

CONCLUSIONS

- Brenipatide demonstrated a distinct profile compared with published profiles of other weekly incretin therapies.
- The half-life of brenipatide and sustained exposure observed across the dosing interval results in a favorable peak-to-trough ratio, supporting once-weekly dosing, which may lead to sustained pharmacological effect and provide favorable gastrointestinal tolerability as observed in this study.
- These data support the selection of weekly maintenance doses across a broad range of BMIs, including normal body weight, that optimize safety, tolerability and incretin pharmacology, in substance use, psychiatric and immunological disorders.



BACKGROUND

- Incretin agonist molecules have been approved for several cardiometabolic disorders
- GIP and GLP-1 receptors are located throughout the body, including the pancreas, gastrointestinal tract, heart, lungs, kidneys, liver, adipose tissue, and brain
 - GIP and GLP-1 receptor agonists may show utility both centrally and peripherally for several indications

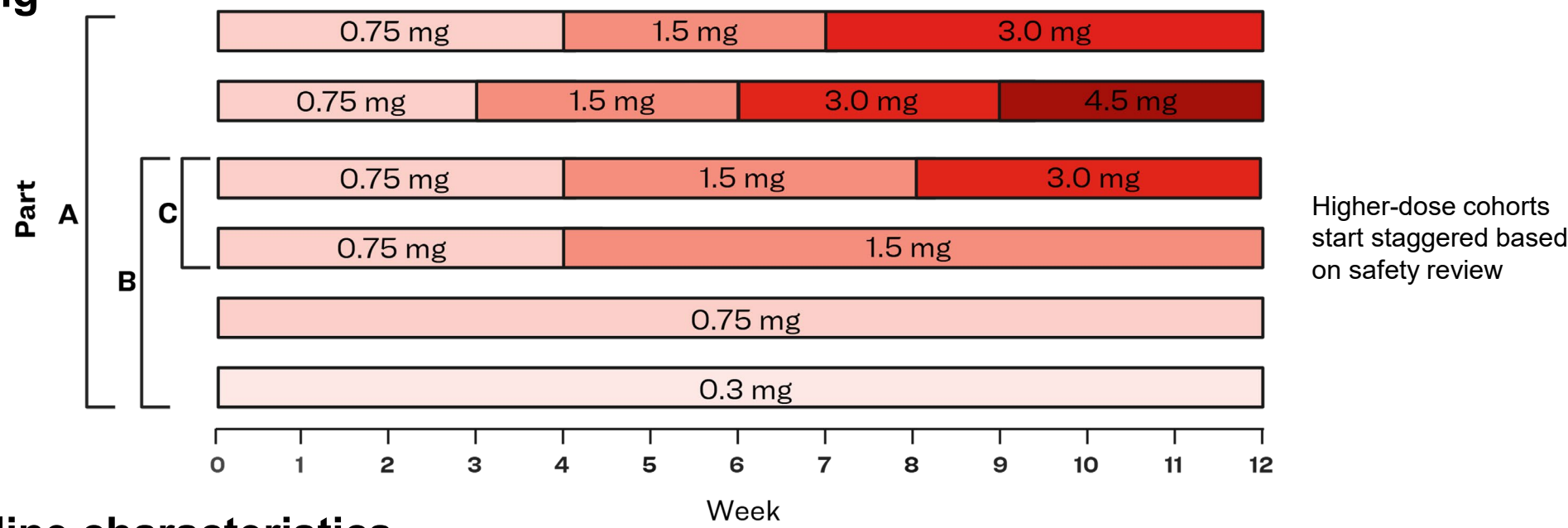
Brenipatide

- A novel long-acting dual GIP/GLP-1 receptor agonist
- Being investigated as a potential treatment for substance use, psychiatric and immunologic disorders

STUDY DESIGN

- NCT06606106 is phase 1, investigator- and participant-blind, multiple ascending dose study of brenipatide with an 8-week follow-up period
- Study population
 - Part A:** Participants with BMIs of 27.0 - 45.0 kg/m²; randomized 16:2
 - Part B:** Participants with BMIs of 22.0 - 26.9 kg/m²; randomized 16:2
 - Part C:** Participants with BMIs of 22.0 - 26.9 kg/m²; Japanese and Chinese ethnicities; randomized 6:2

Dosing



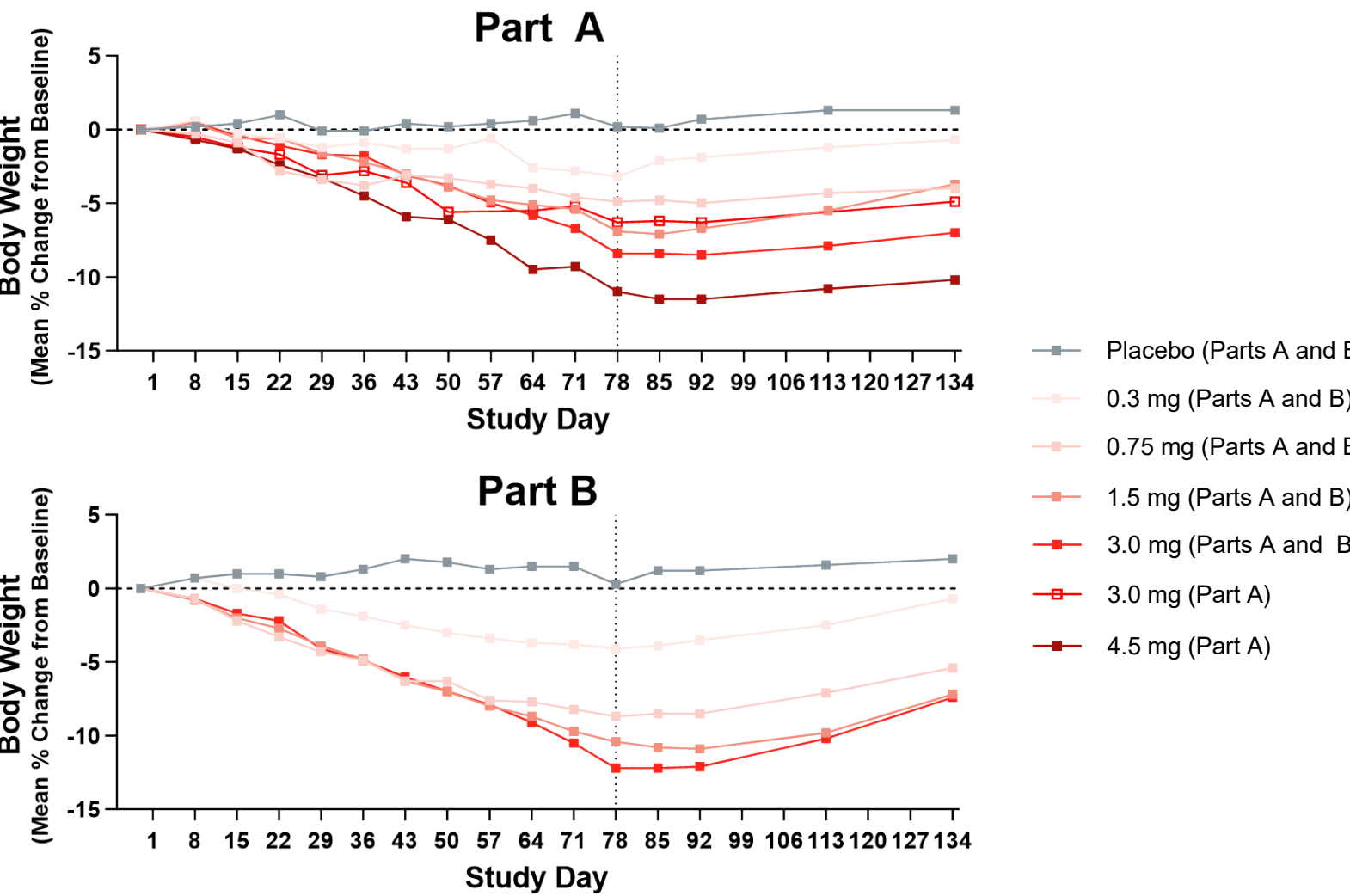
Baseline characteristics

	Part A		Part B		Part C	
	Placebo N=12	Brenipatide N=96 (16/cohort)	Placebo N=8	Brenipatide N=64 (16/cohort)	Placebo N=8	Brenipatide N=24 (6/cohort)
Baseline body weight, mean (SD), kg	101.4 (20.7)	97.5 (17.4)	70.1 (7.6)	75.0 (8.0)	68.6 (5.5)	72.5 (7.0)
BMI, mean (SD), kg/m ²	33.2 (5.5)	32.9 (4.0)	25.2 (1.5)	24.9 (1.3)	24.1 (1.6)	24.9 (1.5)
Female (%)	25.0	22.9	37.5	25.0	0	4.2

PHARMACODYNAMICS

- Dose-responsive incretin pharmacology was confirmed via body weight change as a reliable surrogate to enable dose selection
- Similar PD between ethnicities (Japanese and Chinese – Part C)

Percent change in body weight

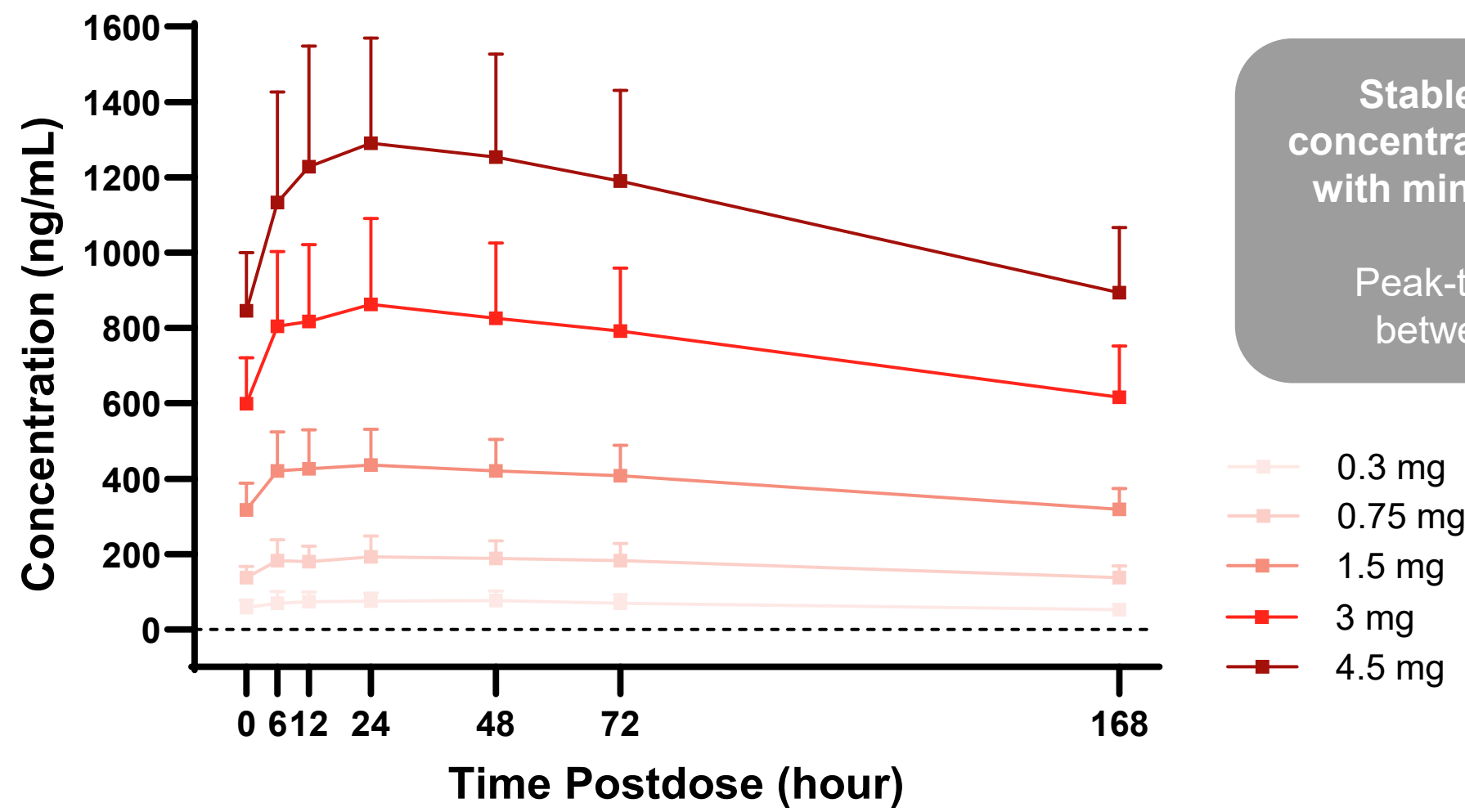


Vertical dotted line indicates the end of dosing on day 78.

PHARMACOKINETICS

- Brenipatide displayed dose-proportional PK
- Similar PK between ethnicities

Brenipatide plasma concentration-time profile after multiple weekly doses



Mean (+SD) following the dose on Day 78 for Part A. Similar results were observed in Parts B and C.

Abbreviations: AE=adverse event; BMI=body mass index; GI=gastrointestinal; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide 1; N=number of participants; nP=number of participants with an adverse event; PD=pharmacodynamics; PK=pharmacokinetics; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event; QW=once-weekly
Note: Interim data are presented from completed cohorts

SAFETY

- Brenipatide was generally well-tolerated across all doses studied in participants with a wide range of BMI and different ethnicities
- No SAEs or deaths were reported
- Four (2.2%) brenipatide-treated participants discontinued the study drug due to a TEAE
- The most frequently reported TEAEs were GI-related
 - overall GI TEAE frequency of 25% in both brenipatide- and placebo-treated participants
 - all TEAEs of nausea, vomiting, and diarrhea were mild except for two moderate nausea events, none resulted in study drug discontinuation
 - numerically lower frequency of GI TEAEs observed in Part A
- Dysesthesia-related TEAEs were reported in 15.2% of brenipatide-treated participants and none on placebo
 - all were mild except for one moderate event
 - all resolved either while still on drug or following the last dose, and only one resulted in study drug discontinuation
 - numerically lower frequency of dysesthesia-related TEAEs observed in Part A

TEAE overview

	Part A		Part B		Part C		Overall	
	Placebo N=12	Brenipatide N=96 (16/cohort)	Placebo N=8	Brenipatide N=64 (16/cohort)	Placebo N=8	Brenipatide N=24 (6/cohort)	Placebo (N=28)	Brenipatide (N=184)
TEAEs, nP (%)	5 (41.7)	35 (36.5)	3 (37.5)	49 (76.6)	4 (50.0)	22 (91.7)	12 (42.9)	106 (57.6)
TEAE severity, nP (%)								
Mild	4 (33.3)	34 (35.4)	3 (37.5)	49 (76.6)	2 (50.0)	22 (91.7)	11 (39.3)	105 (57.1)
Moderate	1(8.3)	4 (4.2)	0	2 (3.1)	1 (12.5)	1 (4.2)	2 (7.1)	7 (3.8)
Severe	0	3 (3.1)	0	0	0	0	0	3 (1.6)
TEAEs leading to discontinuation, nP (%)	0	2 (2.1)	0	2 (3.1)	0	0	0	4 (2.2)
GI-related TEAEs, nP (%)	3 (25.0)	14 (14.6)	1 (12.5)	23 (35.9)	3 (37.5)	9 (37.5)	7 (25.0)	46 (25.0)
Nausea	0	5 (5.2)	1 (12.5)	13 (20.3)	2 (25.0)	4 (16.7)	3 (10.7)	22 (12.0)
Vomiting	0	5 (5.2)	1 (12.5)	2 (3.1)	0	2 (8.3)	1 (3.6)	9 (4.9)
Diarrhea	0	6 (6.3)	1 (12.5)	9 (14.1)	0	6 (25.0)	1 (3.6)	21 (11.4)
Dysesthesia-related TEAEs, nP (%)	0	3 (3.1)	0	15 (23.4)	0	10 (41.7)	0	28 (15.2)

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