Corporate Presentation

GH Research PLC (NASDAQ: GHRS)

February 2024

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Seeking Ultra-Rapid, Durable Remissions in Depression

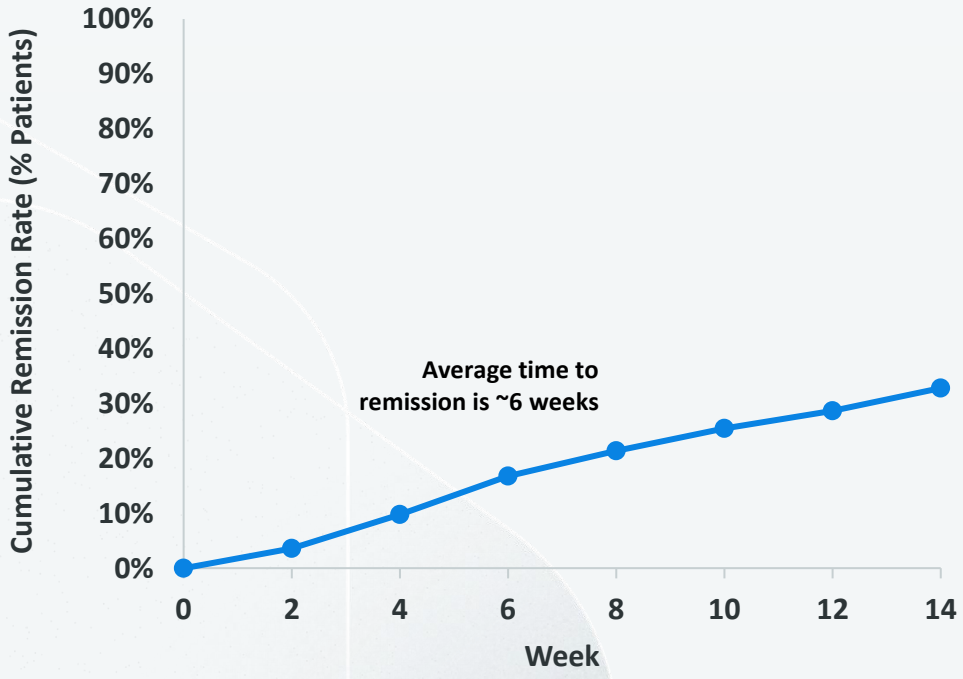
Pipeline

*Bipolar II disorder with a current major depressive episode
5-MeO-DMT, 5-Methoxy-N,N-Dimethyltryptamine; i.v., intravenous; RDBPC, Randomized, Double-Blind, Placebo-Controlled; POC, Proof-of-Concept; HV, Healthy Volunteer

The Problem for Patients with Depression

Established Therapies are Slow-Acting

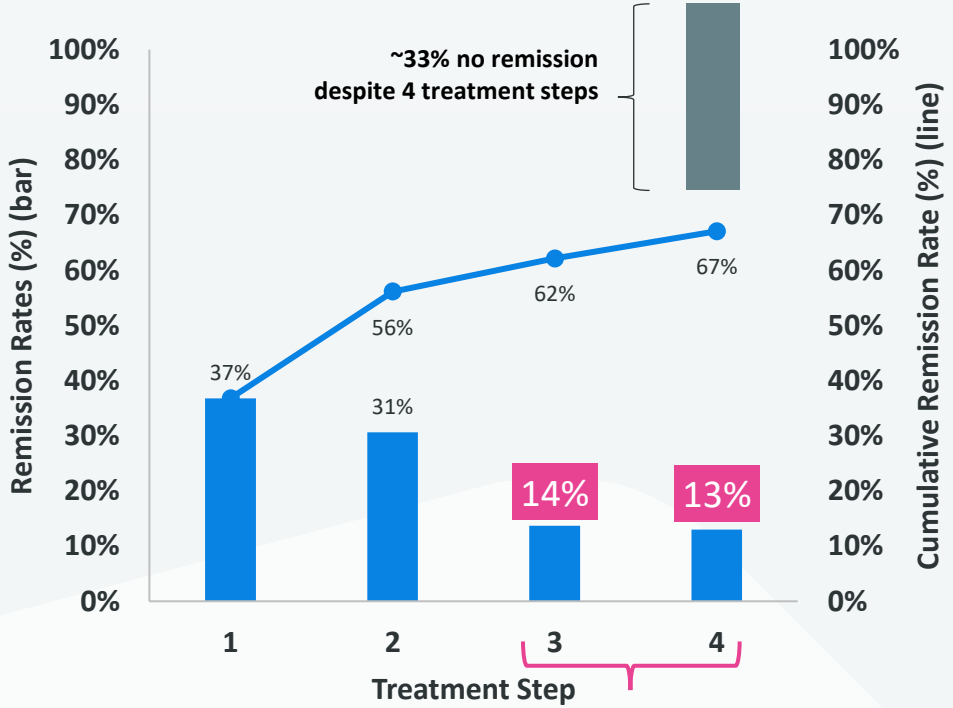
(STAR*D study, Remission Rate Over Time, Treatment Step 1 = Citalopram)



Adapted from Trivedi et al., Am J Psychiatry 2006 and Rush et al., Am J Psychiatry 2006
TRD, Treatment-Resistant Depression

... Remission Rates in TRD < 15%

(STAR*D study, Remission Rates Treatment Steps 1 to 4)



2 or more prior therapies = TRD

Large and Open Depression Market in the EU and US

First Line MDD

- Diagnosed: ~**48M**
  - Treated (pharmacotherapy ± psychotherapy): ~**24M**

Second Line MDD

- Non-response to first line: ~**13M**

Treatment-Resistant Depression (TRD)

- Non-response to two prior lines: **~9M**

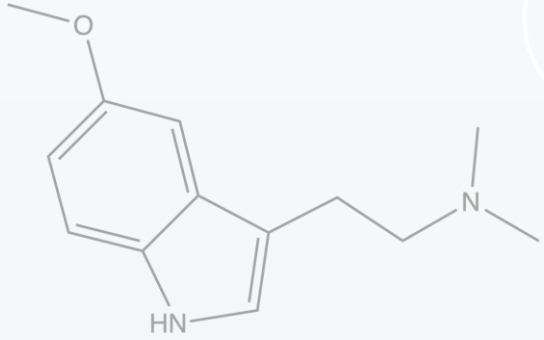
Patients cycle through ineffective therapies for TRD

*Company estimates based on: https://www.nimh.nih.gov/health/statistics/major-depression.shtml; Wittchen et al., The size and burden of mental disorders and other disorders of the brain in Europe 2010, European Neuropsychopharmacology (2011); Rush et al., Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report, Am J Psychiatry 2006*
MDD, Major Depressive Disorder

Mebufotenin (5-MeO-DMT) and GH001

Mebufotenin (5-Methoxy-N,N-Dimethyltryptamine, 5-MeO-DMT)

- Naturally-occurring psychoactive substance from tryptamine class
- **Highly potent** agonist on 5-HT1A and 5-HT2A receptors



Mebufotenin (5-MeO-DMT)

GH001 (Mebufotenin administration via a proprietary pulmonary inhalation approach)

- **Psychoactive effects with ultra-rapid onset** (within seconds) **and short duration** (5 to 30 min)
- **High propensity to induce peak experiences (PE), which may be a surrogate marker for therapeutic effects**
- **Intraday individualized dosing regimen (IDR)** for **maximization of ultra-rapid and durable remissions**
- **Single visit initial treatment,** without additional mandated visits for psychotherapy or psychological support before or after dosing
- Potential for **convenient and infrequent retreatment**

Foundational IP


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
27 August 2020 (27.08.2020)
WIPO | PCT
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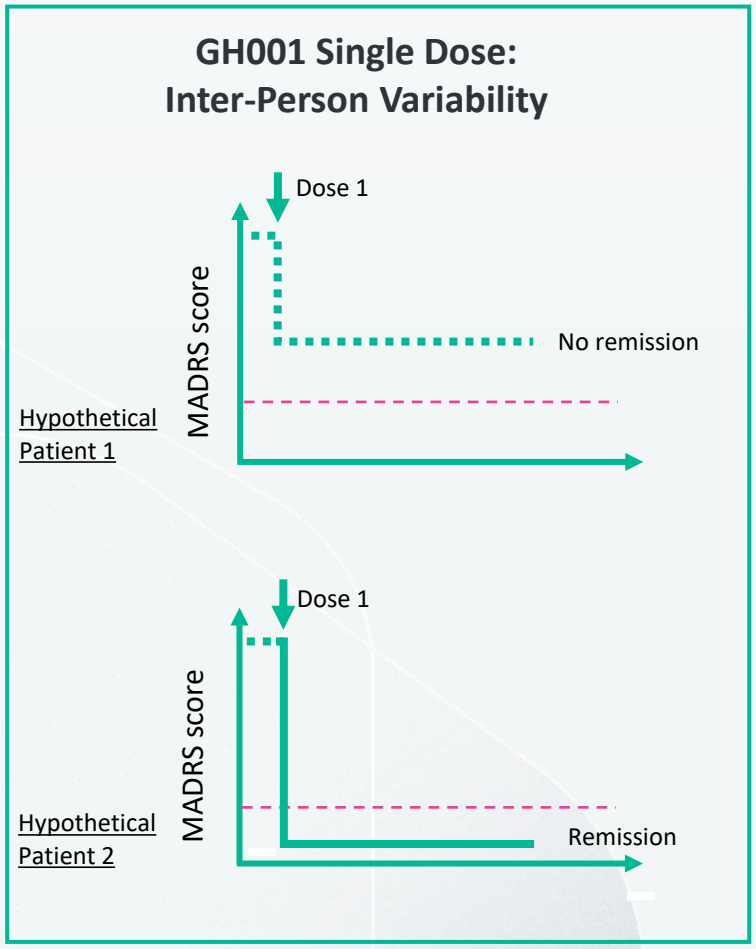
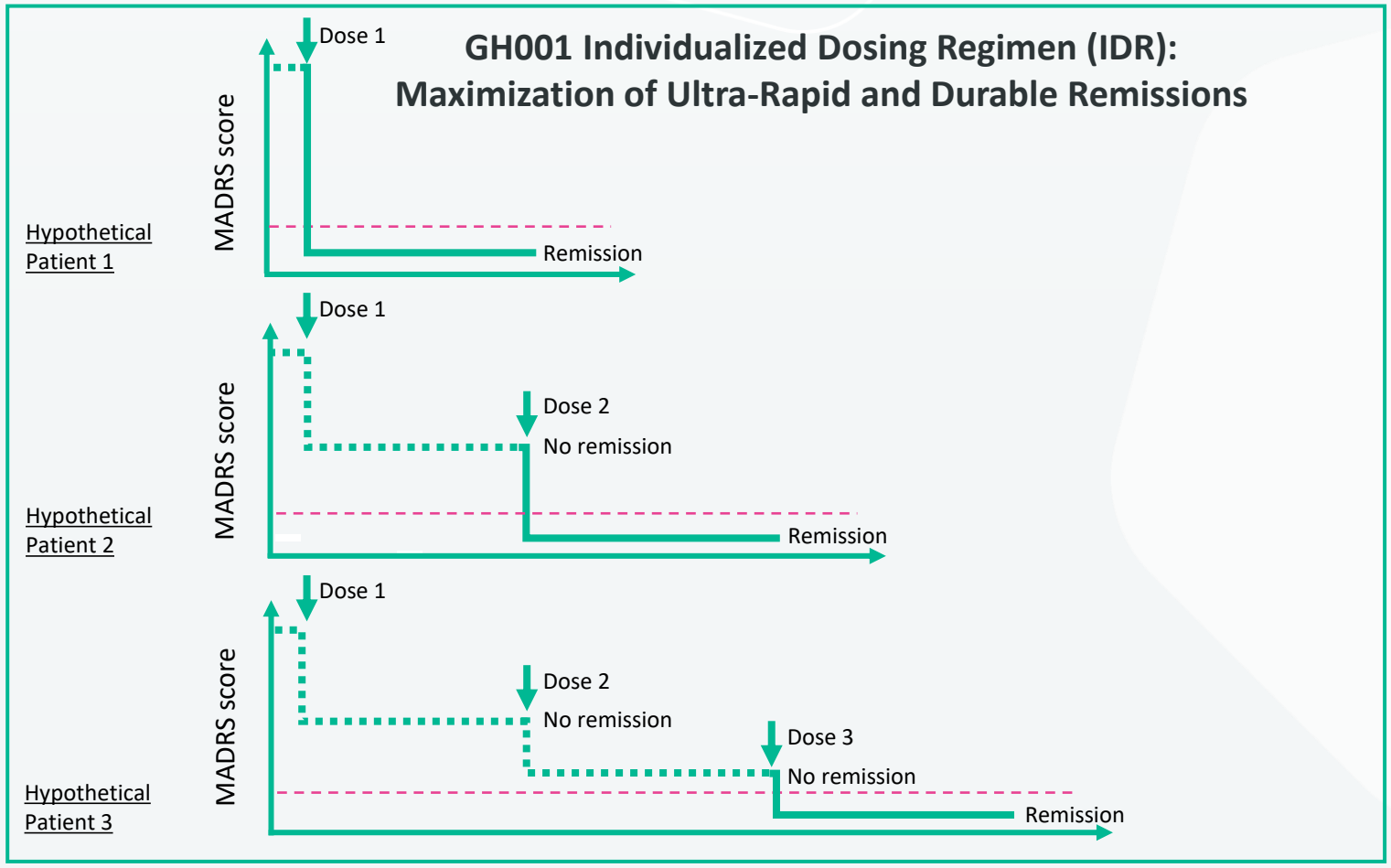
GH001 – Individualized Dosing Regimen (IDR) for Maximization of Ultra-Rapid and Durable Remissions





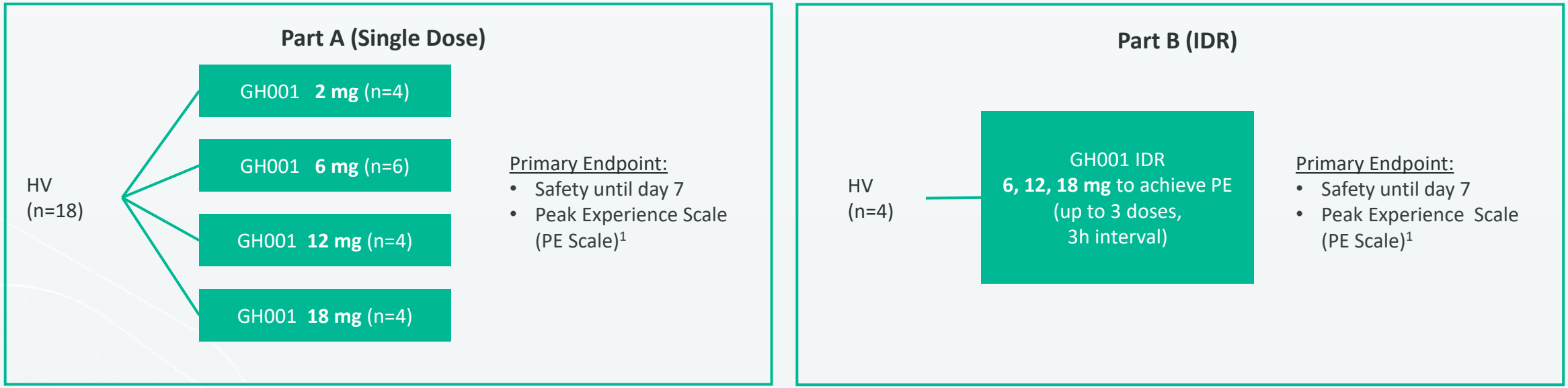
MADRS, Montgomery-Åsberg Depression Rating Scale

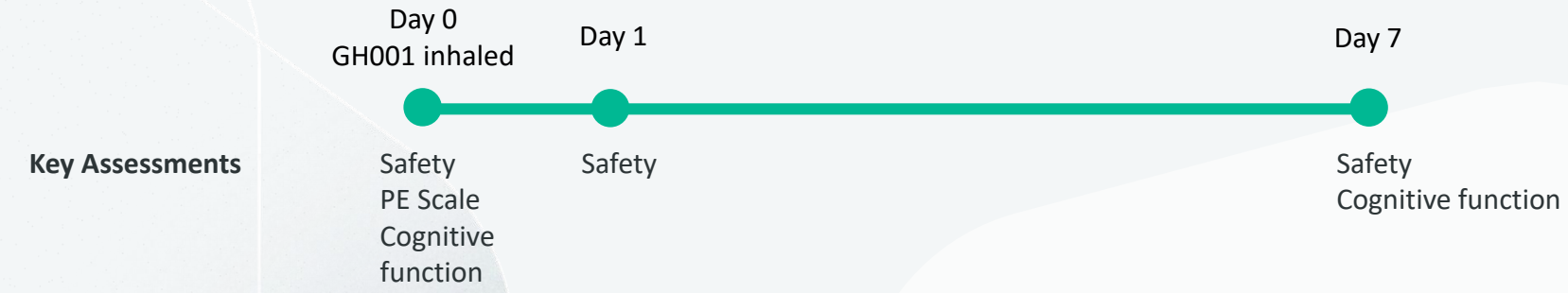
Phase 1 Trial of GH001 in Healthy Volunteers GH001-HV-101

(Completed)

Clinicaltrials.gov ID: NCT04640831

Design of Phase 1 Trial of GH001 in Healthy Volunteers (GH001-HV-101)





HV, Healthy Volunteer; PE, Peak Experience; IDR, Individualized Dosing Regimen

[1]The PE Scale averages answers scored by the subject by marking a visual analogue scale between 0 and 100 for the following three questions: 1. How intense was the experience; 2. To what extent did you lose control; 3. How profound (i.e., deep and significant) was the experience?

Part A (Single Dose) and Part B (IDR) – Safety

Study Safety Group review

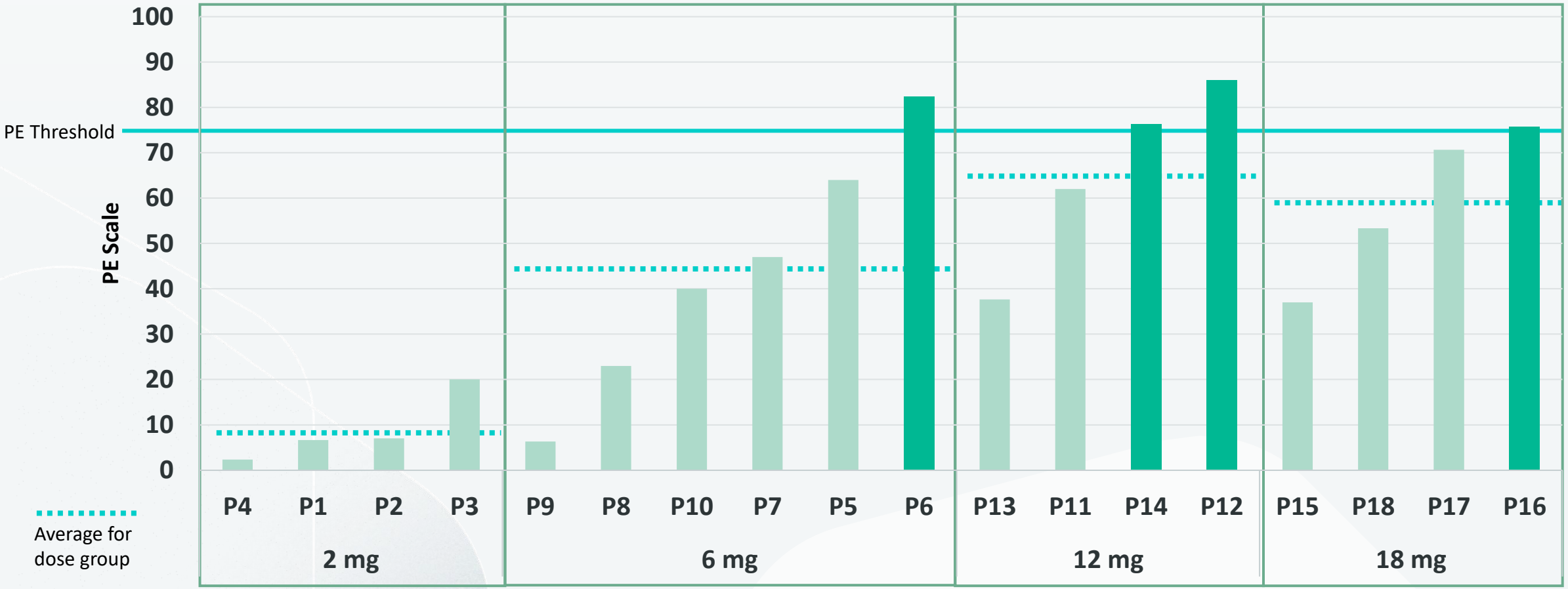
- **No SAEs**
- **All ADRs mild, except two moderate** (*)
- **All ADRs resolved spontaneously**
- **Inhalation well-tolerated**
- No noteworthy changes in vital parameters, except for temporary, non-clinically relevant increase in heart rate and blood pressure shortly after administration of GH001
- No clinically relevant changes in safety laboratory analyses, psychiatric symptom scales or measures of cognitive function

ADRs	Part A (Single Dose)				Part B (IDR)
	2 mg (n=4)	6 mg (n=6)	12 mg (n=4)	18 mg (n=4)	IDR[1] (n=4)
MedDRA Preferred Term	Number of Events				
Abnormal dreams				1	
Anxiety		1	1		
Clumsiness		1			
Confusional state		1			
Euphoric mood		1			
Fatigue				1	1*
Feeling hot		1			
Flashback				1	
Hallucination				1	
Head discomfort					1
Headache		2		1	1
Heart rate increased			1*		
Hyperacusis				1	
Insomnia				1	
Mental fatigue				1	
Nausea	2	1		1	2
Vision blurred	1				

SAE, Serious Adverse Event; ADR, Adverse Drug Reaction, an adverse event with a relationship code to the investigational product of definite, probable, or possible, or where code is missing; IDR, Individualized Dosing Regimen

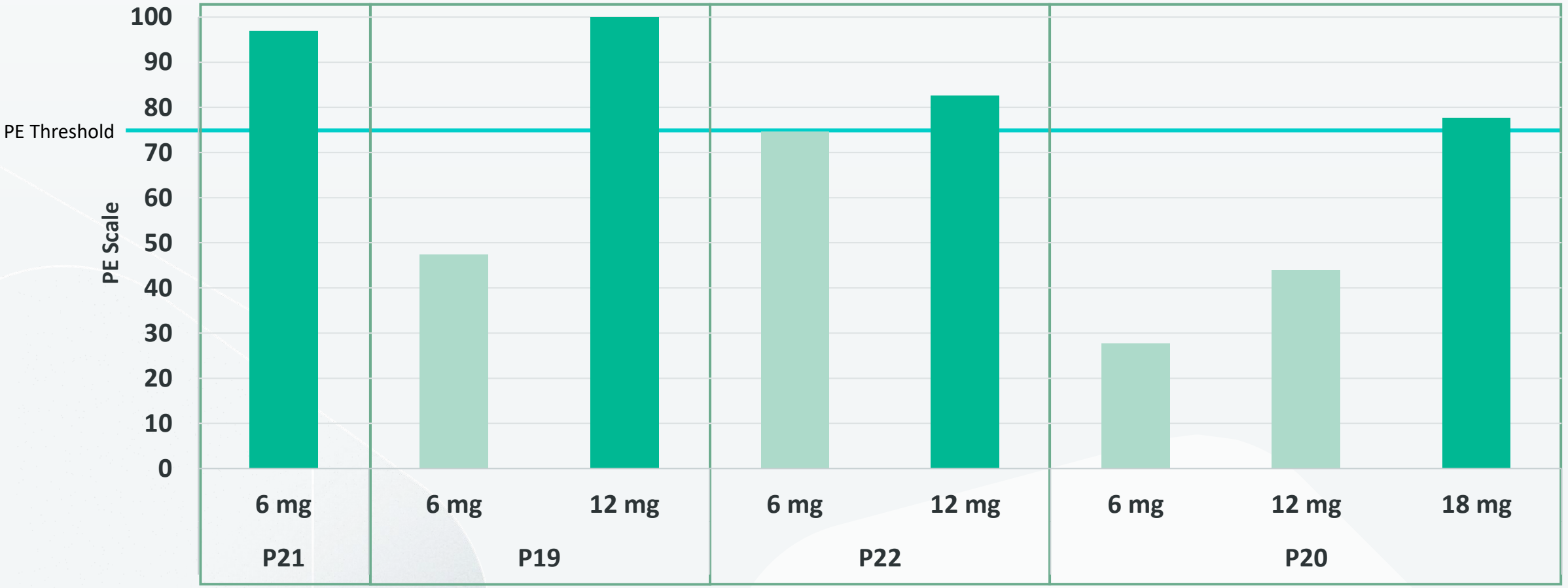
[1]6 mg (n=1); 6-12 mg (n=2); 6-12-18 mg (n=1)

Part A – Peak Experience (PE) Dose-Effects and Inter-Person Variability



PE, Peak Experience

Part B – Peak Experience (PE)
Effect of Intraday Individualized Dosing Regimen (IDR)



PE, Peak Experience

Phase 1/2 Trial of GH001 in Treatment-Resistant Depression GH001-TRD-102

(Completed)

Clinicaltrials.gov ID: NCT04698603

Design of Phase 1/2 Trial of GH001 in TRD (GH001-TRD-102)

Phase 1 (Single Dose)

TRD[1] (n=8)

- GH001 **12 mg** (n=4)
- GH001 **18 mg** (n=4)

Primary Endpoint:
- Safety until day 7

Phase 2 (IDR)

TRD[1] (n=8)

GH001 IDR
6, 12, 18 mg to achieve PE
(up to 3 doses,
3h interval)

Primary Endpoint:
- MADRS remission day 7 (MADRS≤10)

	Day 0 GH001 inhaled	Day 1	Day 7
Key Assessments	MADRS H2 PE Scale Safety	MADRS D1 Cognitive function Safety	MADRS D7 Cognitive function Safety

TRD, Treatment-Resistant Depression; PE, Peak Experience; MADRS, Montgomery-Åsberg Depression Rating Scale;
IDR, Individualized Dosing Regimen; H, Hour; D, Day

[1]Defined as inadequate response to at least two adequate courses of pharmacological therapy or one adequate course of pharmacological therapy and at least one adequate course of evidence-based psychotherapy

Phase 1 (Single Dose) and Phase 2 (IDR) – Safety

Study Safety Group review

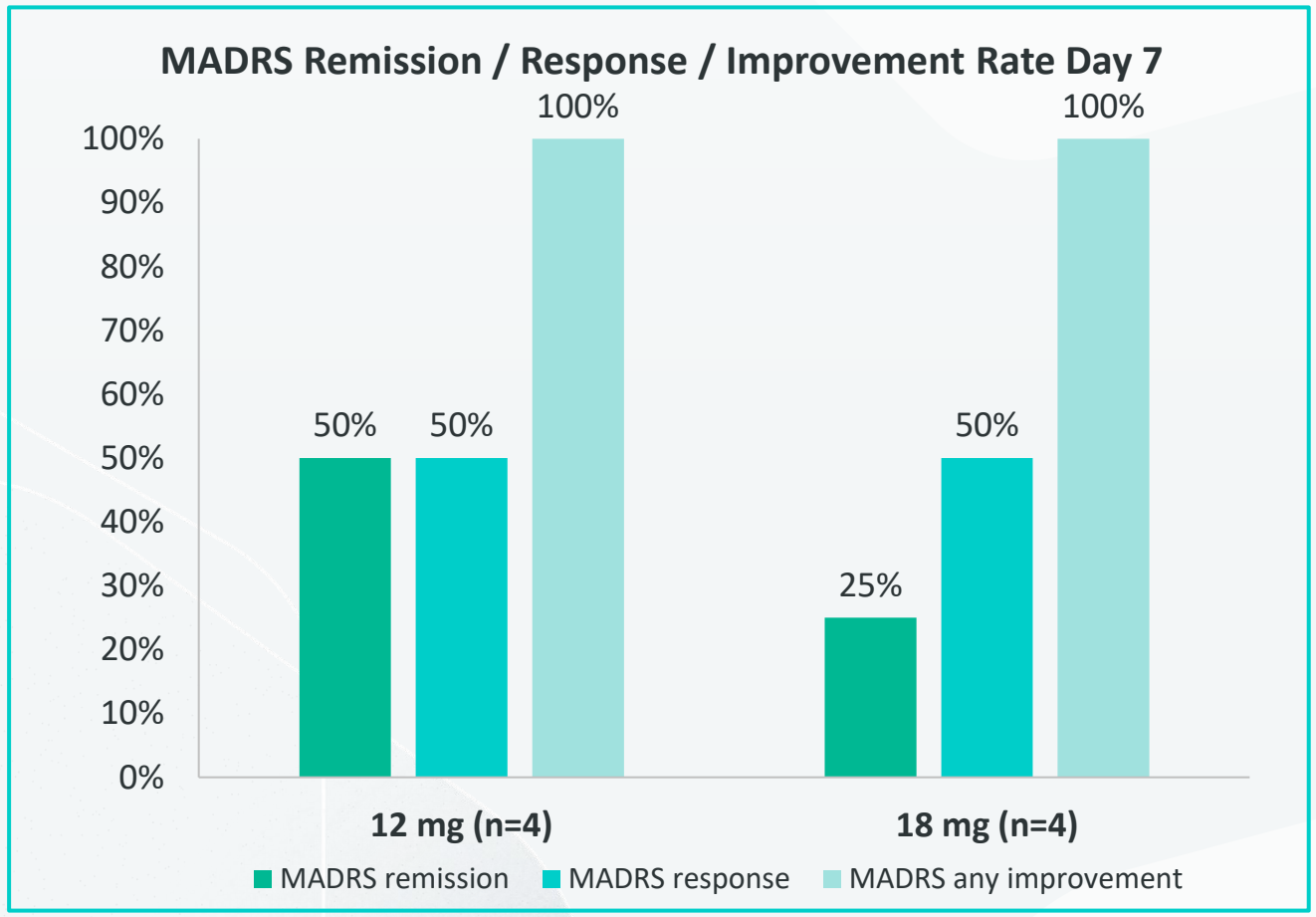
- **No SAEs**
- **All ADRs mild, except three moderate** (*)
- **All ADRs resolved spontaneously**
- **Inhalation well-tolerated**
- No noteworthy changes in vital parameters, except for temporary, non-clinically relevant increase in heart rate and blood pressure shortly after administration of GH001
- No clinically relevant changes in safety laboratory analyses, psychiatric safety assessments or measures of cognitive function
- No safety signal relating to suicidal ideation or suicidal behavior, based on C-SSRS and MADRS subscore item “suicidal thoughts”

ADRs	Phase 1 (Single Dose)		Phase 2 (IDR)
	12 mg (n=4)	18 mg (n=4)	IDR[1] (n=8)
MedDRA Preferred Term	Number of Events		
Abdominal discomfort			1
Anxiety			2
Depressive symptom			1*
Dizziness	1		
Feeling abnormal	1	1	
Flashback	1	1	2
Headache	2	1	3
Muscle discomfort			1
Muscle spasms		1	
Nausea			2*
Paresthesia			1
Sensory disturbance			3

SAE, Serious Adverse Event; ADR, Adverse Drug Reaction, an adverse event with a relationship code to the investigational product of definite, probable, or possible, or where code is missing; IDR, Individualized Dosing Regimen; C-SSRS, Columbia-Suicide Severity Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale

[1]6-12 mg (n=6); 6-12-18 mg (n=2)

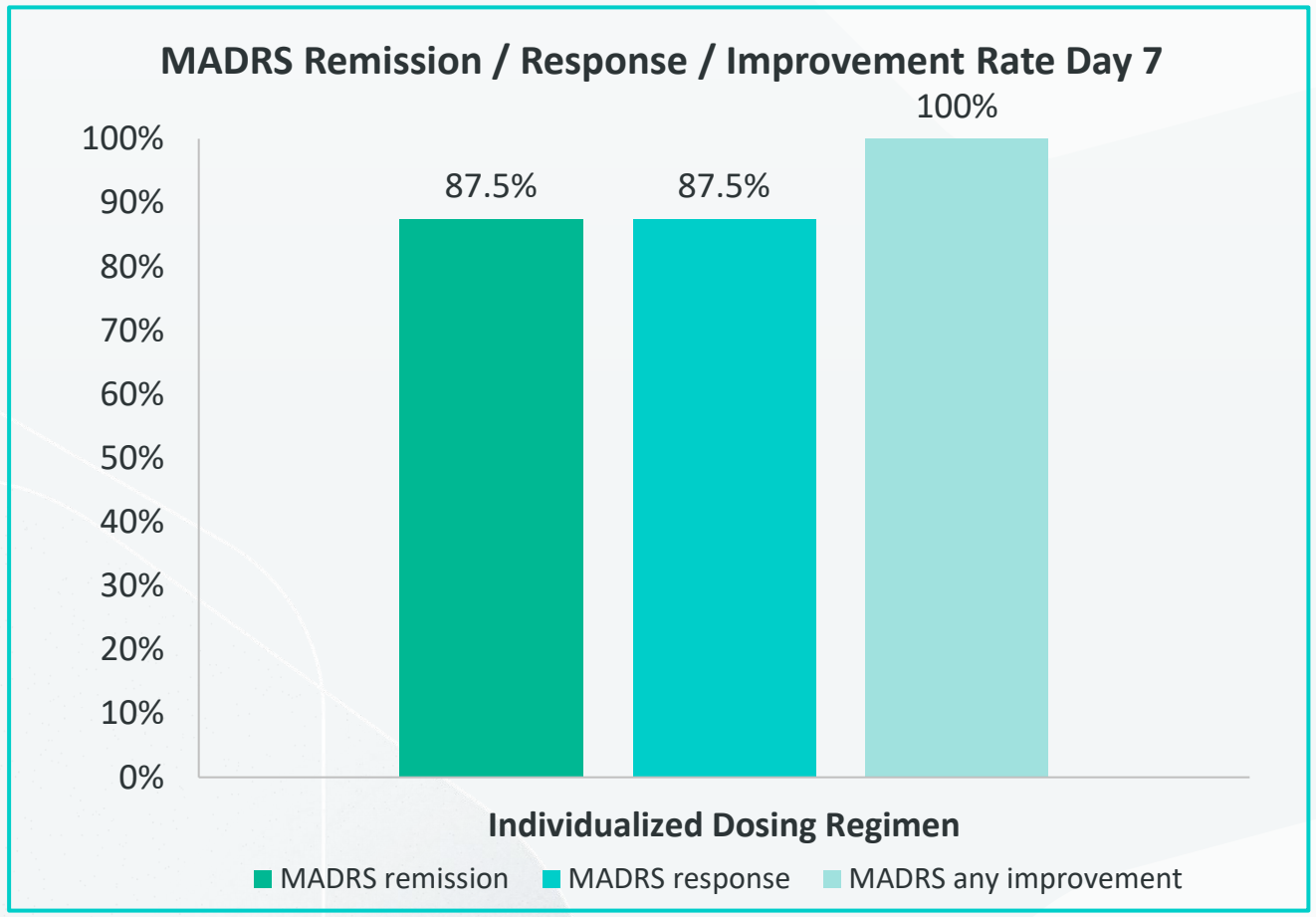
Phase 1 (Single Dose) – Efficacy (MADRS)



- 2 of 4 (50%) in the 12 mg group and 1 of 4 (25%) in the 18 mg group had a MADRS remission at day 7
- 2 of 8 patients had a PE and both had a MADRS remission at day 7

PE, Peak Experience; MADRS, Montgomery–Åsberg Depression Rating Scale
MADRS remission = MADRS of ≤10; MADRS response = Reduction of ≥50% from baseline in MADRS; MADRS any improvement = any reduction from baseline in MADRS

Phase 2 (IDR) – Efficacy (MADRS)



- **Primary endpoint met:**
  7 of 8 patients (87.5%) had a MADRS remission at day 7, p<0.0001
- 7 of 8 patients had a PE and 6 of those had a MADRS remission at day 7

PE, Peak Experience; MADRS, Montgomery–Åsberg Depression Rating Scale
MADRS remission = MADRS of ≤10; MADRS response = Reduction of ≥50% from baseline in MADRS; MADRS any improvement = any reduction from baseline in MADRS

Phase 2 (IDR) – Efficacy (MADRS Change from Baseline)

- **Primary endpoint met:**
  7 of 8 patients (87.5%) had a MADRS remission at day 7, p<0.0001
- 7 of 7 remissions from day 1 and 4 of 7 remissions from 2 hours

[1]*Baseline mean MADRS=32*

MADRS and PE – Observed Improved Outcome in Phase 2 (IDR) vs Phase 1 (Single Dose)

	Phase 2 (IDR)	Phase 1 (Single Dose) 12 mg	Phase 1 (Single Dose) 18 mg
MADRS Remission Rate Day 7	87.5% (7 of 8)	50% (2 of 4)	25% (1 of 4)
Mean MADRS Change Day 7	-24.4 (-76%)	-21.0 (-65%)	-12.5 (-40%)
Rate of PE	87.5% (7 of 8)	50% (2 of 4)	0% (0 of 4)
Mean PE Score	90.4 (at final dose)	58.2	59.1

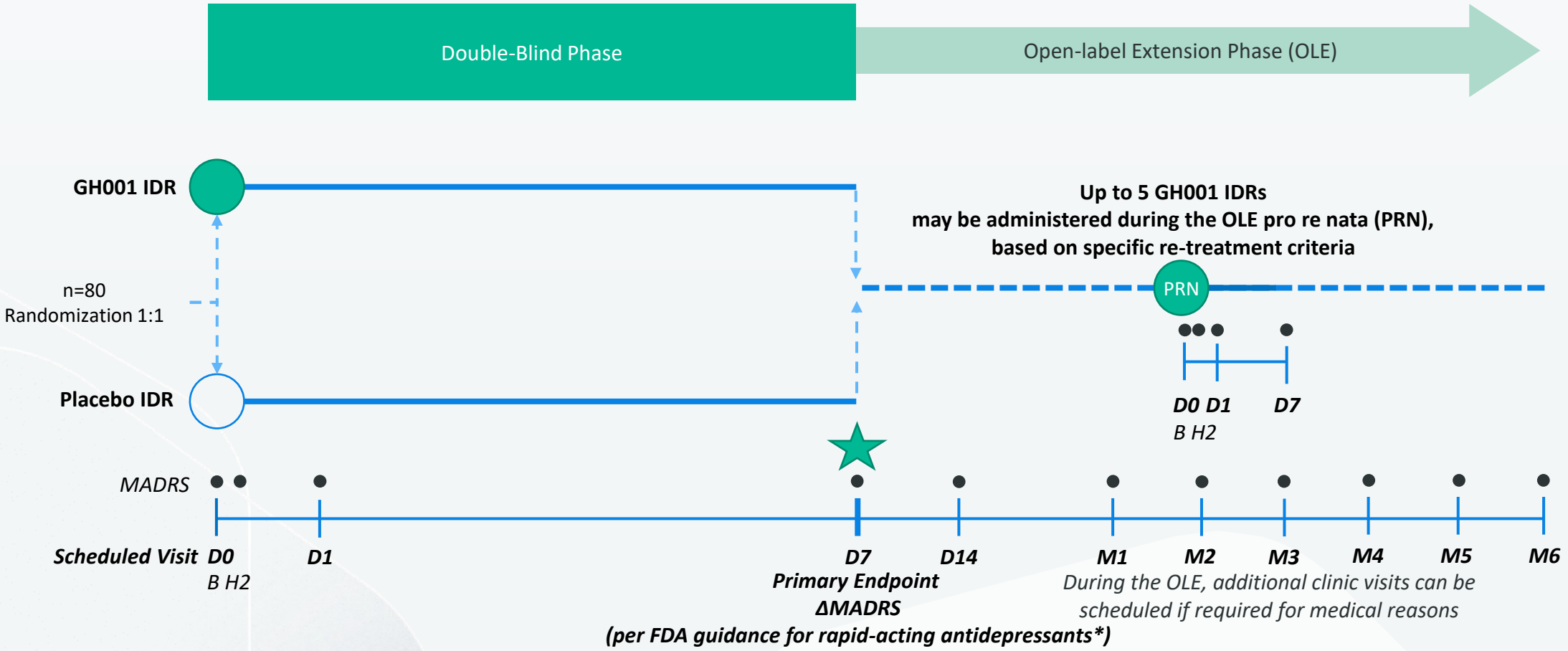
PE, Peak Experience; MADRS, Montgomery-Åsberg Depression Rating Scale; IDR, Individualized Dosing Regimen

Phase 2b Trial in Treatment-Resistant Depression GH001-TRD-201

(Initiated)

EudraCT Number: 2022-000574-26

Design of Phase 2b Trial in TRD (GH001-TRD-201)



*The bold solid lines indicate the fixed duration of 7 days (± 1 day) after an IDR with visits on D0, D1 and D7. The bold dotted line indicates the variable duration until a potential GH001 IDR in the OLE. The GH001 IDR consists of up to 3 increasing doses (6, 12, 18 mg) and the Placebo IDR consists of up to three placebo doses, to achieve a peak experience, given at a 1H interval. As in previously completed trials, the GH001-TRD-201 trial will be conducted under the supervision of a healthcare provider, but without any planned psychotherapeutic interventions before, during, or after dosing. IDR, Individualized Dosing Regimen; PRN, pro re nata (as needed); B, Baseline; H, Hour; D, Day; M, Month. *FDA draft guidance for industry "Major Depressive Disorder: Developing Drugs for Treatment"*

Three-Layer Protection Strategy

LAYER 1: REGULATORY EXCLUSIVITY

FDA: 5 years (+2.5 years paragraph IV stay)

EMA: 10 years (+1 year for new indication)

LAYER 2: PATENTS

Granted patents and patent applications relating to mebufotenin (5-MeO-DMT), including:

- Novel uses in various disorders (including inhaled, nasal, buccal, sublingual, i.v., i.m., s.c. routes)
- Novel aerosol compositions of matter
- Novel manufacturing methods and novel salt forms
- Novel device-related aspects

LAYER 3: TECHNICAL

Complex bioequivalence for systemically-acting inhalation/intranasal products with high intra- and inter-subject variability

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Anticipated Milestones and Financial Overview

GH001

- Complete double-blind phase of European multi-center, randomized, double-blind, placebo-controlled Phase 2b trial in TRD in Q3 2024, and provide top-line data in Q3 or Q4 2024
- Complete Phase 2a trial in PPD and provide top-line data in Q3 2024
- Provide update on U.S. IND clinical hold and planned Phase 1 clinical pharmacology trial with proprietary aerosol delivery device in Q2 2024

GH002

- Complete analysis of Phase 1 clinical pharmacology trial in healthy volunteers

GH003

- Complete preclinical development

Financial Overview

- Cash, cash equivalents, other financial assets and marketable securities were $222.7 million as of December 31, 2023
- We believe existing cash, cash equivalents, other financial assets and marketable securities will be sufficient to fund operating expenses and capital expenditure requirements into 2026

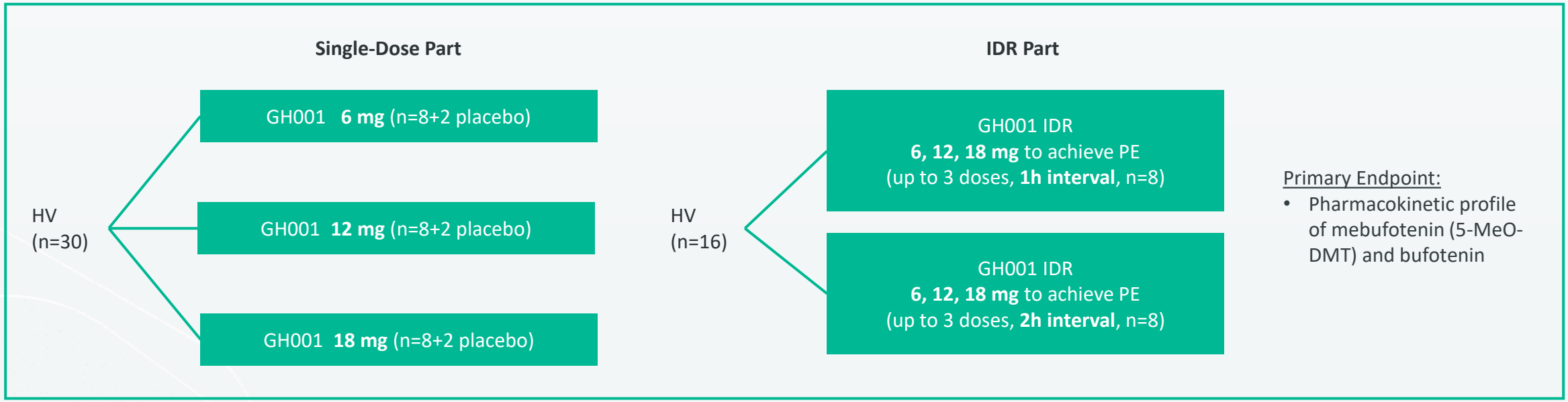
Appendix
Additional Completed Trials

Phase 1 Clinical Pharmacology Trial of GH001 in Healthy Volunteers GH001-HV-103

(Completed)

Clinicaltrials.gov ID: NCT05163691

Design of Phase 1 Clinical Pharmacology Trial of GH001 in Healthy Volunteers (GH001-HV-103)



HV, Healthy Volunteer; PE, Peak Experience; IDR, Individualized Dosing Regimen

Single Dose and IDR – Safety and Further Results

Safety Review

- **No SAEs**
- **All ADRs mild**
- **All ADRs resolved spontaneously**
- **Inhalation well-tolerated**
- No noteworthy changes in vital parameters, except for temporary, non-clinically relevant increase in heart rate and blood pressure shortly after administration of GH001
- No clinically relevant changes in ECG, safety laboratory analyses, peak flow, cognitive function or psychiatric symptom scales, including the C-SSRS

Further Results

- Pharmacokinetic analyses and psychoactive effect assessments (PE Scale) support that an interval down to 1 hour between individual doses of the IDR is feasible for future clinical trials

ADRs	Single-dose				IDR	
	6 mg (n=8)	12 mg (n=8)	18 mg (n=8)	Placebo (n=6)	1h interval (n=8)[1]	2h interval (n=8)[2]
MedDRA Preferred Term	Number of Events					
Abnormal dreams						1
Chest discomfort		1				
Crying			2		2	
Dizziness			1			
Dry mouth	1					
Dyskinesia			1			
Fatigue		1			2	1
Headache	3		1		1	1
Hypoesthesia oral		1				
Paresthesia oral						1
Retching			1			
Somnolence		1				
Tachycardia			2			
Tension						1
Tremor			1			

SAE, Serious Adverse Event; Adverse Drug Reaction, or ADR, an adverse event with a relationship code to the investigational product of definite, probable, or possible, or where code is missing; IDR, Individualized Dosing Regimen; C-SSRS, Columbia-Suicide Severity Rating Scale; PE, Peak Experience

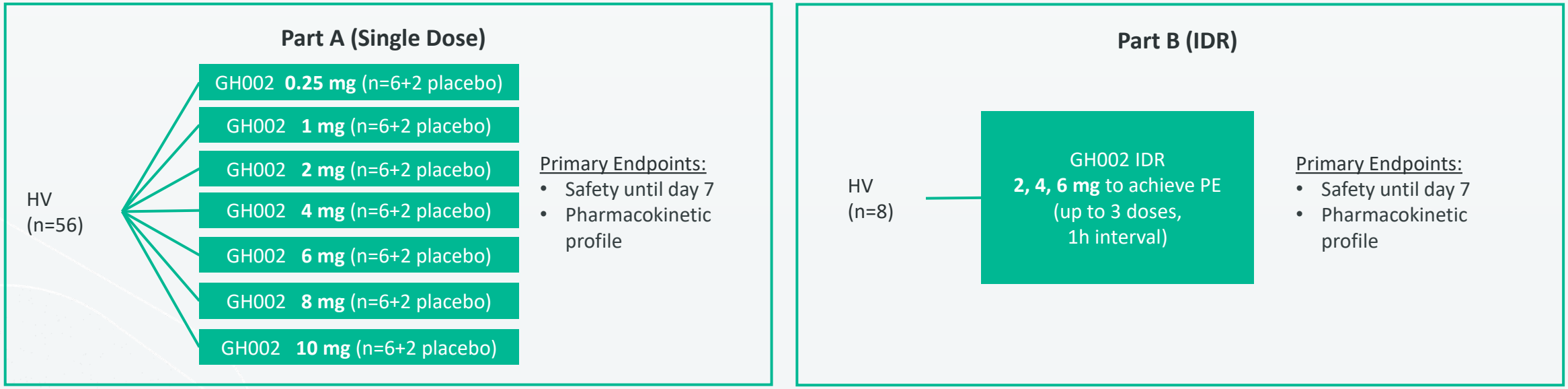
[1]6 mg (n=1), 6-12 mg (n=3); 6-12-18 mg (n=4)
[2]6-12 mg (n=3); 6-12-18 mg (n=5)

Phase 1 Clinical Pharmacology Trial of GH002 in Healthy Volunteers GH002-HV-105

(Completed)

Clinicaltrials.gov ID: NCT05753956

Design of Phase 2 Trial of GH002 in Healthy Volunteers (GH002-HV-105)



HV, Healthy Volunteer; PE, Peak Experience; IDR, Individualized Dosing Regimen

Single Dose and IDR – Safety and Further Results

Safety review

- **No SAEs**
- **All ADRs mild, except one moderate (*)**
- No noteworthy changes in vital parameters, except for temporary, non-clinically relevant increase in heart rate and blood pressure shortly after administration of GH002
- No clinically relevant changes in ECG and safety laboratory analyses
- No clinically relevant changes in psychiatric symptoms scales, except for changes associated with the ADRs of emotional distress and poor quality sleep

Further Results

- Potent psychoactive effects (PsE) with ultra-rapid onset and short duration were observed. The pharmacokinetic profile correlated with the ultra-rapid profile of the PsE.

ADRs	Single Dose								IDR
	0.25 mg (n=6)	1 mg (n=6)	2 mg (n=6)	4 mg (n=6)	6 mg (n=6)	8 mg (n=6)	10 mg (n=6)	Placebo (n=14) [1]	1h interval (n=8) [2]
MedDRA Preferred Term	Number of Events								
Abnormal dreams							1		
Body temperature increased			1						
Chest discomfort				1					
Cold sweat				1					
Dizziness			2	1		1			
Dyspnoea									1
Emotional distress			1			1*			
Fatigue			2		1	1	1		
Grunting							2		
Headache					1			1	2
Head discomfort				1		1			1
Muscle spasms							2		
Muscle twitching							1		
Nausea	1	1		2		1			2
Neck pain							1		
Pain in extremity							2		
Poor quality sleep							1		
Sleep disorder							1		
Vomiting		1				1	1		1

[1] *n=2 subjects received placebo in each dose group*
[2] *2 mg (n=4); 2-4 mg (n=2); 2-4-6 mg (n=2)*

SAE, Serious Adverse Event; Adverse Drug Reaction, or ADR, an adverse event with a relationship code to the investigational product of definite, probable, or possible, or where code is missing; IDR, Individualized Dosing Regimen

Seeking Ultra-Rapid, Durable Remissions in Depression