GH Research

Corporate Presentation

GH Research PLC (NASDAQ: GHRS)

October 2021

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GH Research

Seeking Ultra-Rapid, Durable Remissions in Depression

Status

- GH Research was founded in 2018
  - Seed Finance, 2018: Founders, BVF Partners LP
  - Series A, 2020: BVF Partners LP, Founders
  - Series B, 2021: RA Capital (co-lead), RTW Investments LP (co-lead), alongside other new investors, BVF Partners LP and Founders / Board of Directors
  - IPO, 2021 NASDAQ: GHRS

  → Total capital raised: 315M USD

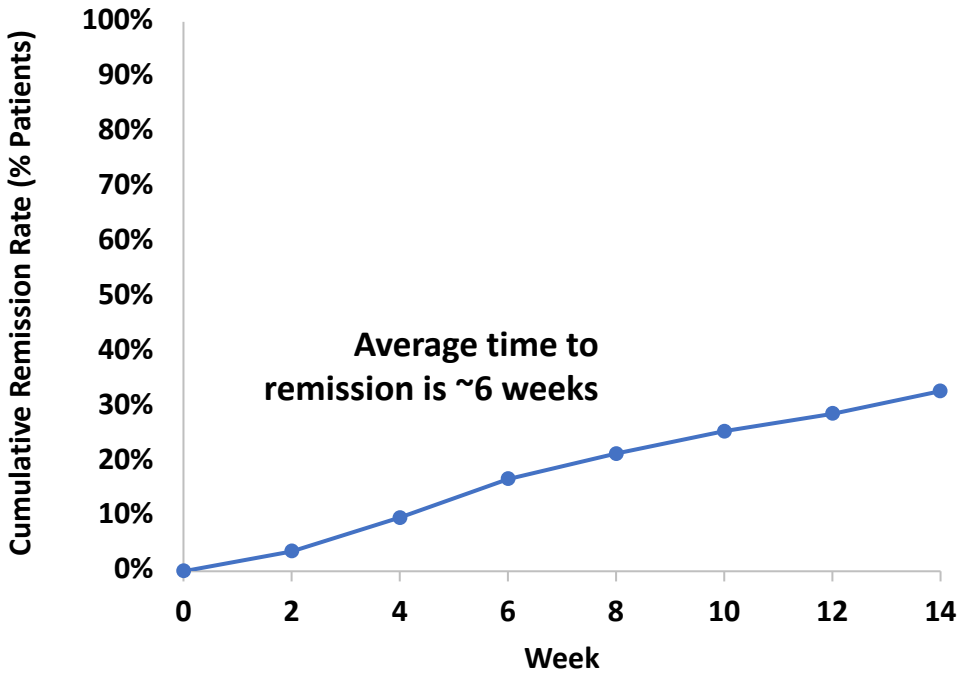
- GH001 (5-MeO-DMT for inhalation) is core focus
  - Completed Phase 1 trial in Healthy Volunteers
  - Ongoing Phase 1 clinical pharmacology trial in Healthy Volunteers, expected completion 4Q 2021
  - Ongoing Phase 1/2 trial in Treatment-Resistant Depression (TRD), expected completion 4Q 2021
  - Planning randomized, controlled Phase 2b trial in TRD
  - Planning Phase 2a trials in two new indications

- GH002 (5-MeO-DMT for injection)
  - Ongoing preclinical development

The Problem for Patients with Depression

Established Therapies are Slow-Acting

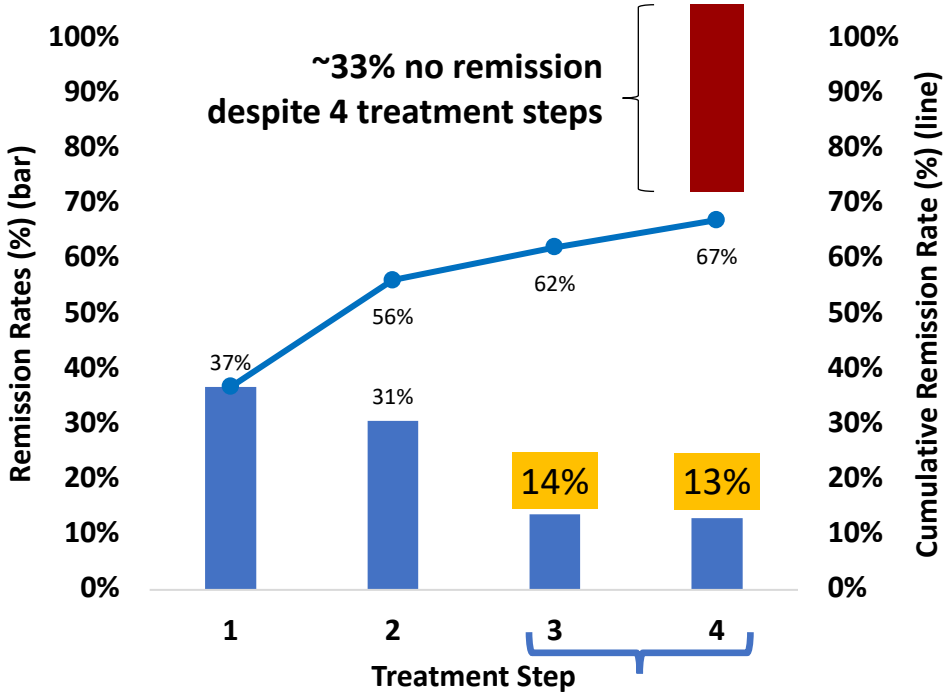
(STAR*D study, Remission Rate Over Time, Treatment Step 1 = Citalopram)



Adapted from Trivedi et al., Am J Psychiatry 2006 and Rush et al., Am J Psychiatry 2006

... Remission Rates in TRD < 15%

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



2 or more prior therapies = Treatment-Resistant Depression (TRD)

Large and Open Depression Market 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)

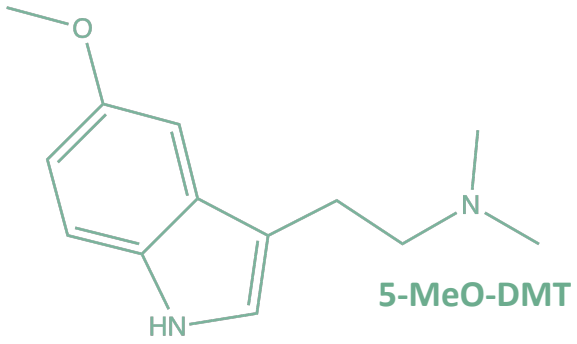
- Non-response to two prior lines: **~9M**

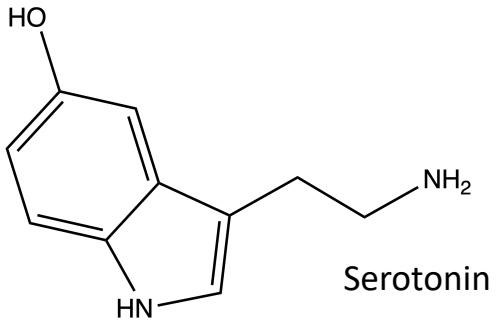
Patients cycle through ineffective therapies for TRD

*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*

5-MeO-DMT and GH001

- 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine)
  - Naturally-occurring psychoactive substance from tryptamine class
  - Structural analogue to serotonin
  - Highly potent agonist on 5-HT1A and 5-HT2A receptors
  - **Psychoactive effects with ultra-rapid onset (within seconds) and short-lived (5 to 30 min)**
  - **High propensity to induce peak experiences (PE), which may be a surrogate marker for therapeutic effects**
  - Proposed mode of action: Normalization (re-set) of disturbed resting-state network connectivity





- GH001
  - Innovative drug product for 5-MeO-DMT administration via a proprietary inhalation approach

GH001 – Individualized Dosing Regimen Could Achieve Ultra-Rapid and Durable Remissions

The ultra-rapid action and short half-life of GH001 allows

- Repeated administration **within the same day**
- **Maximization of remissions**
- **Single visit initial treatment, with no structured psychotherapy** required

Foundational IP


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
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WIPO | PCT
(10) International Publication Number
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(51) International Patent Classification:
A61K 31/4045 (2006.01) *A61P 25/24* (2006.01)
(21) International Application Number:
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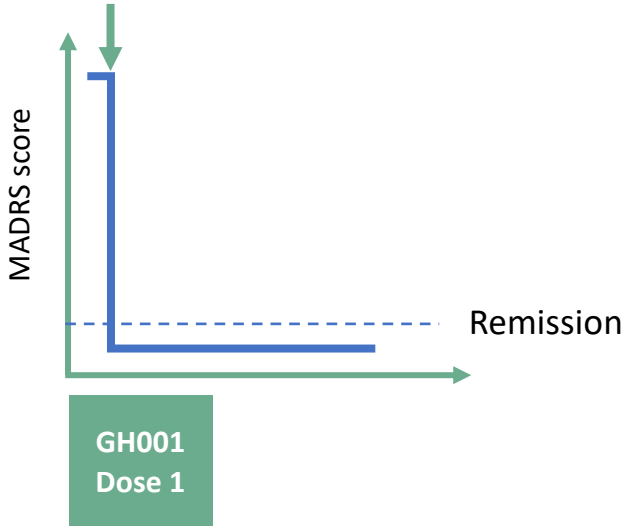
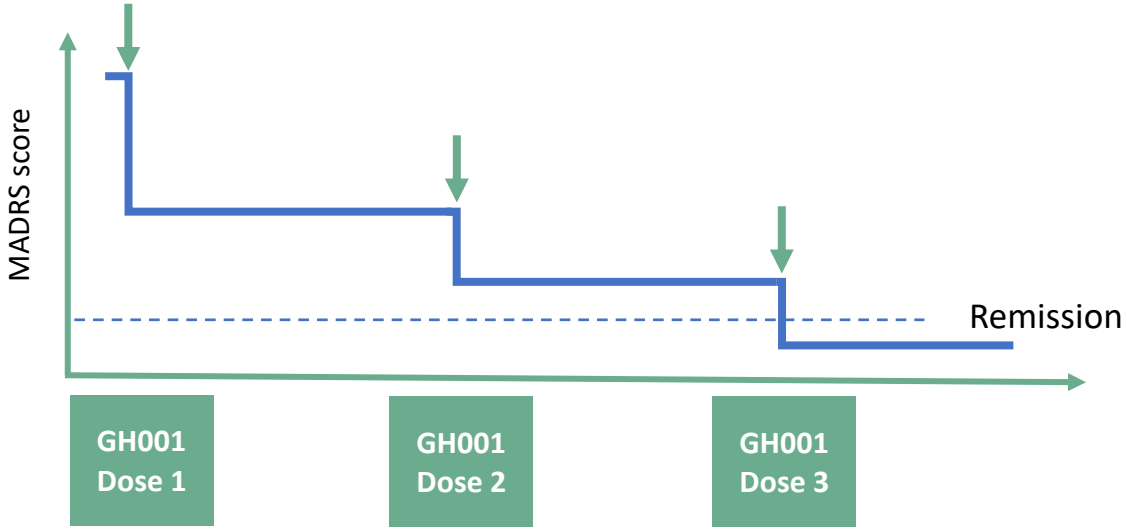
A61K 31/4045 (2006.01) *A61P 25/24* (2006.01)
(21) International Application Number:
PCT/EP2020/054804

Hypothetical Patient 1



Hypothetical Patient 2



Phase 1 Trial in Healthy Volunteers
GH001-HV-101

(completed)

GH001-HV-101; Clinicaltrials.gov ID NCT04640831

Design of Phase 1 Trial in Healthy Volunteers

Part A

HV (n=18)

- GH001 **2 mg** (n=4)
- GH001 **6 mg** (n=6)
- GH001 **12 mg** (n=4)
- GH001 **18 mg** (n=4)

Primary Endpoint:

- Safety until day 7
- Peak Experience Scale (PE Scale)[1]

Part B

HV (n=4)

GH001 Intraday Uptitration Regimen **6, 12, 18 mg** to achieve PE (up to 3 doses)

Primary Endpoint:

- Safety until day 7
- Peak Experience Scale (PE Scale)[1]

	GH001 Administration	Day 1	Day 7
Key Assessments	Safety PE Scale Cognitive function	Safety	Safety Cognitive function

PE, peak experience

[1]*The PE Scale averages answers scored by the patient 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 and B – Primary Endpoint Safety

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Part A - Adverse Drug Reactions

2 mg (n=4)	Day 0	Day 1	Day 7
Nausea	2		
Vision blurred	1		
6 mg (n=6)	**Day 0**	**Day 1**	**Day 7**
Anxiety	1		
Clumsiness		1	
Feeling hot		1	
Headache	1	1	
Nausea	1		
Euphoric mood		1	
Confusional state		1	
12 mg (n=4)	**Day 0**	**Day 1**	**Day 7**
Anxiety	1		
Heart rate increased	1*		
18 mg (n=4)	**Day 0**	**Day 1**	**Day 7**
Nausea	1		
Headache	1		
Hyperacusis		1	
Mental fatigue		1	
Flashback			1
Hallucination		1	
Abnormal dreams		1	
Insomnia		1	
Fatigue		1	

Part B - Adverse Drug Reactions

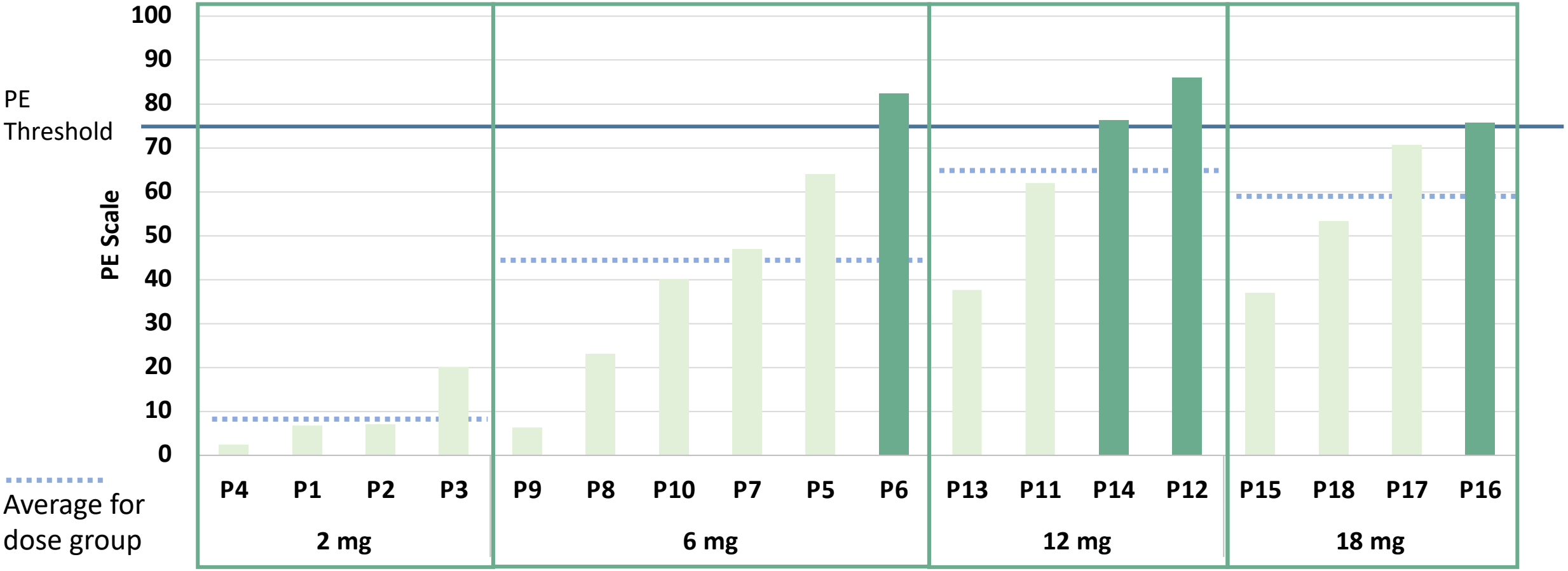
6 mg (n=4)	Day 0	Day 1	Day 7
Nausea	1		
12 mg (n=3)	**Day 0**	**Day 1**	**Day 7**
Headache	1		
Fatigue	1*		
Head discomfort	1		
Nausea	1		
18 mg (n=1)	**Day 0**	**Day 1**	**Day 7**

Study Safety Group review

- **All ADRs mild, except two moderate (*)**
- **All ADRs resolved spontaneously**
- **No SAEs reported**
- **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 significant changes in safety laboratory analyses, psychiatric safety assessments or measures of cognitive function

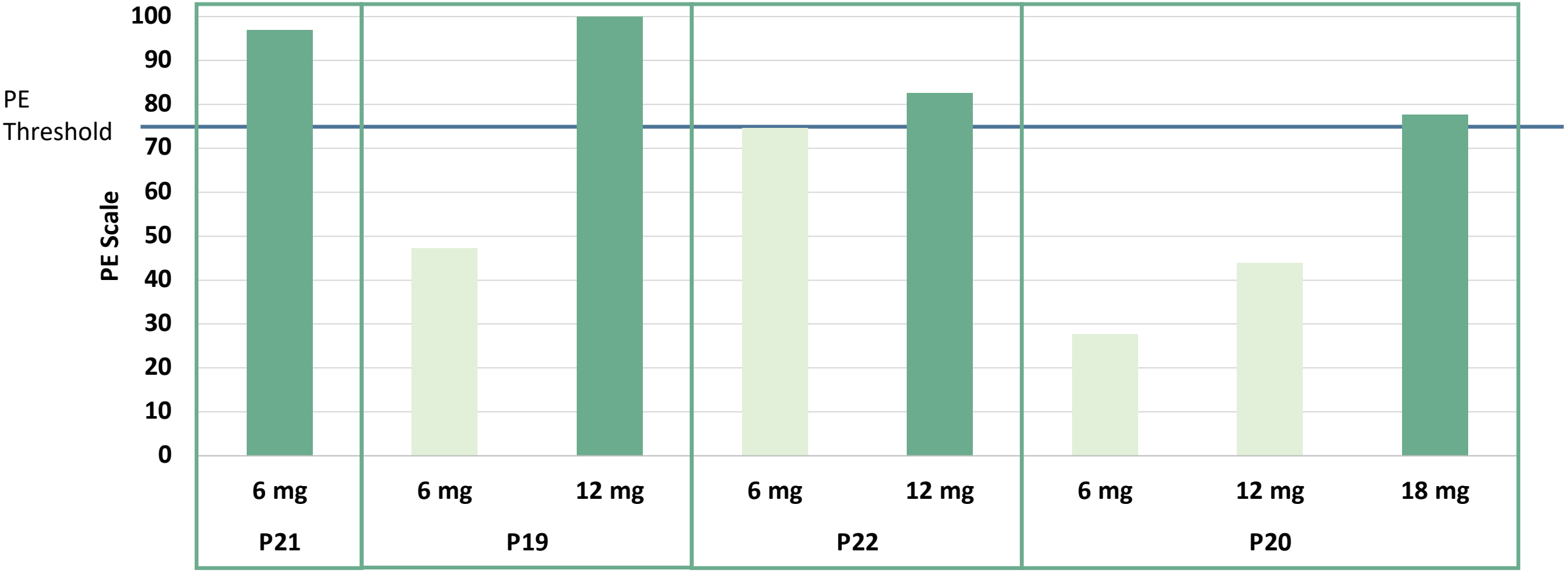
Adverse Drug Reaction, or ADR, an adverse event with a relationship code to the investigational product of definite, probable, or possible, or where code is missing

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



PE, peak experience

Part B – Peak Experience (PE)
Effect of Intraday Uptitration



PE, peak experience

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

(ongoing)

GH001-MDD-102; Clinicaltrials.gov ID NCT04698603

Design of Ongoing Phase 1/2 Trial in TRD

Phase 1, Part A
(Completed)

TRD[1] (n=8)

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

Primary Endpoint:
- Safety until day 7

Phase 2, Part B
(Ongoing)

TRD[1] (n=8)

GH001 Intraday Uptitration Regimen **6, 12, 18 mg** to achieve PE (up to 3 doses)

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

	GH001 Administration	Day 1	Day 7
Key Assessments	MADRS 2-hrs PE Scale Safety	MADRS 1-day Cognitive function Safety	MADRS 7-day Cognitive function Safety

PE, peak experience; MADRS, Montgomery-Åsberg Depression Rating Scale

[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, Part A – Primary Endpoint Safety

Adverse Drug Reactions

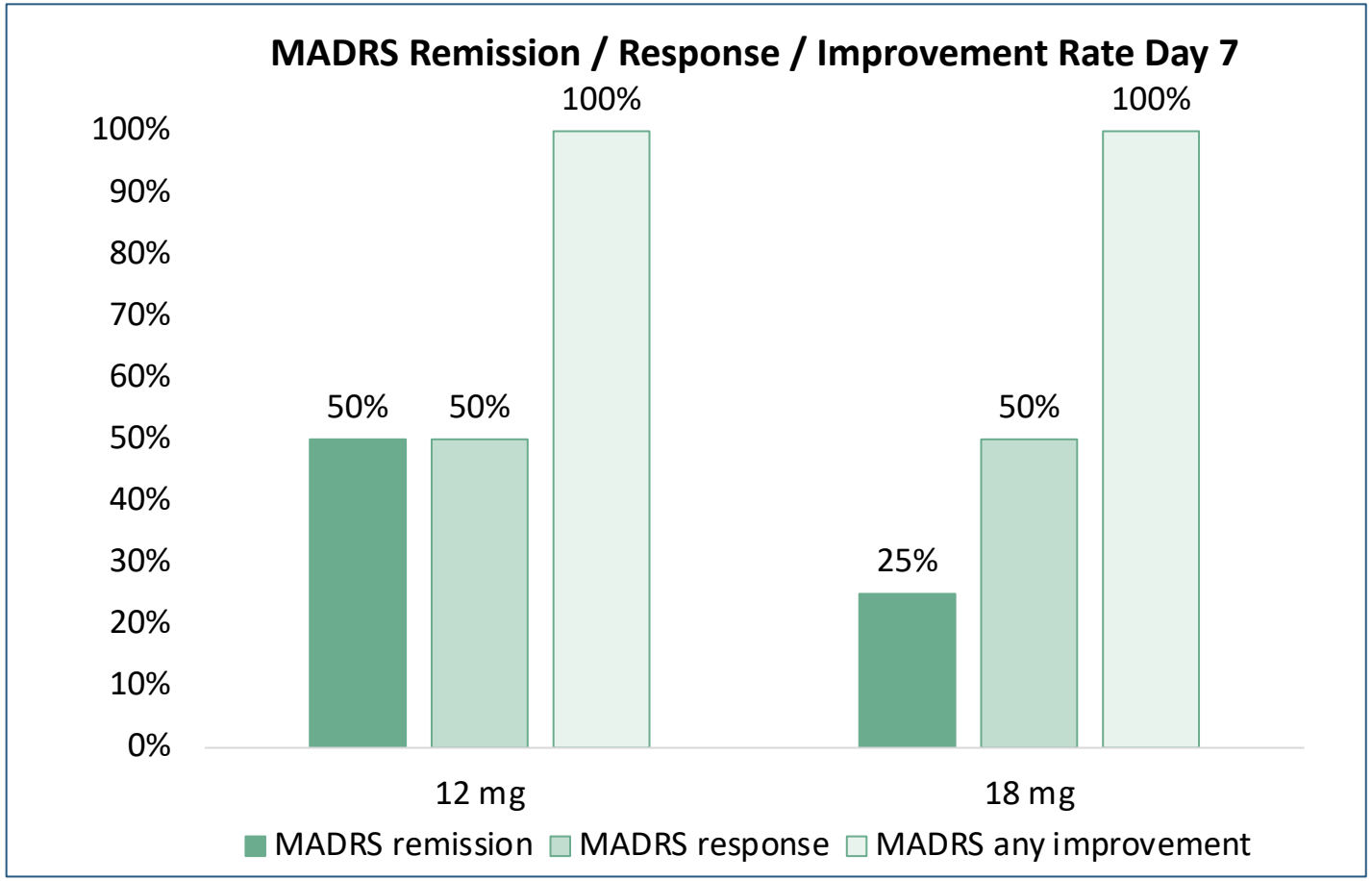
12 mg (n=4)	Day 0	Day 1	Day 7
Dizziness	1		
Headache		2	
Flashback		1	
Feeling abnormal			1
18 mg (n=4)	**Day 0**	**Day 1**	**Day 7**
Feeling abnormal	1		
Muscle spasms	1		
Headache		1	
Flashback		1	

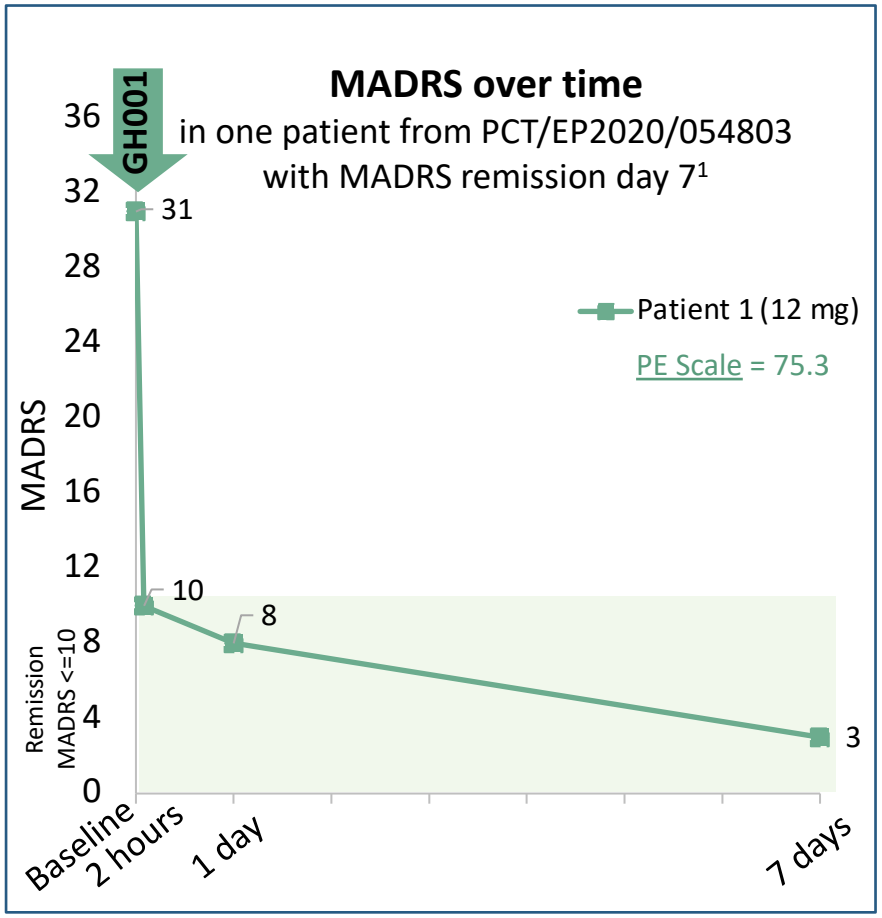
Study Safety Group review

- **All ADRs mild**
- **All ADRs resolved spontaneously**
- **No SAEs reported**
- **Inhalation well-tolerated**
- No clinically significant changes in safety laboratory analyses, vital signs, psychiatric safety assessments or measures of cognitive function

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

Phase 1, Part A – Ultra-Rapid and Durable Remissions After a Single Dose



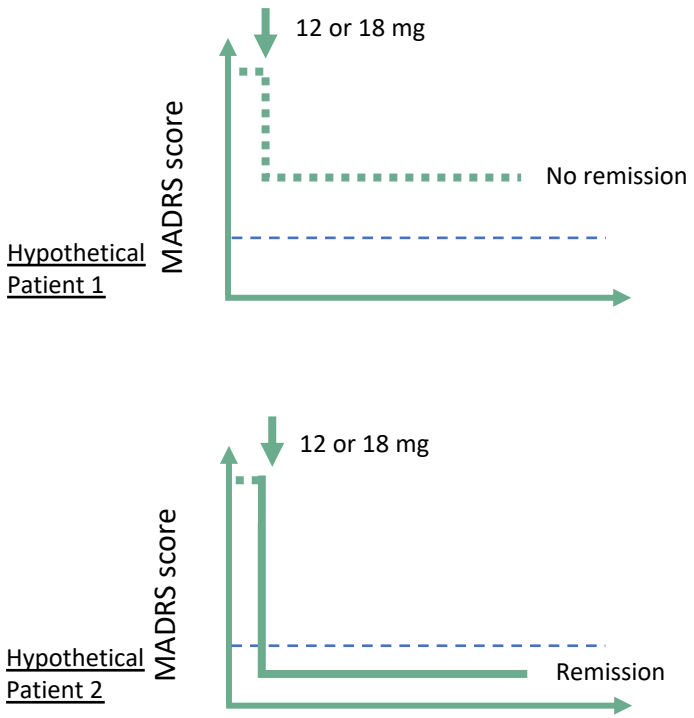


MADRS, Montgomery–Åsberg Depression Rating Scale; MADRS remission = MADRS of ≤10; MADRS response = Reduction of ≥50% from baseline in MADRS. [1]Data is for one patient in Part A with a MADRS remission on day 7 as reported in patent application PCT/EP2020/054803. In total three patients in Part A achieved a remission and one patient achieved a MADRS response on day 7. The other four patients also improved on day 7, but did not achieve a MADRS remission or response. All patients in Part A with a PE achieved a MADRS remission.

Phase 2, Part B – Intraday Uptitration to Potentially Further Increase Remission Rate

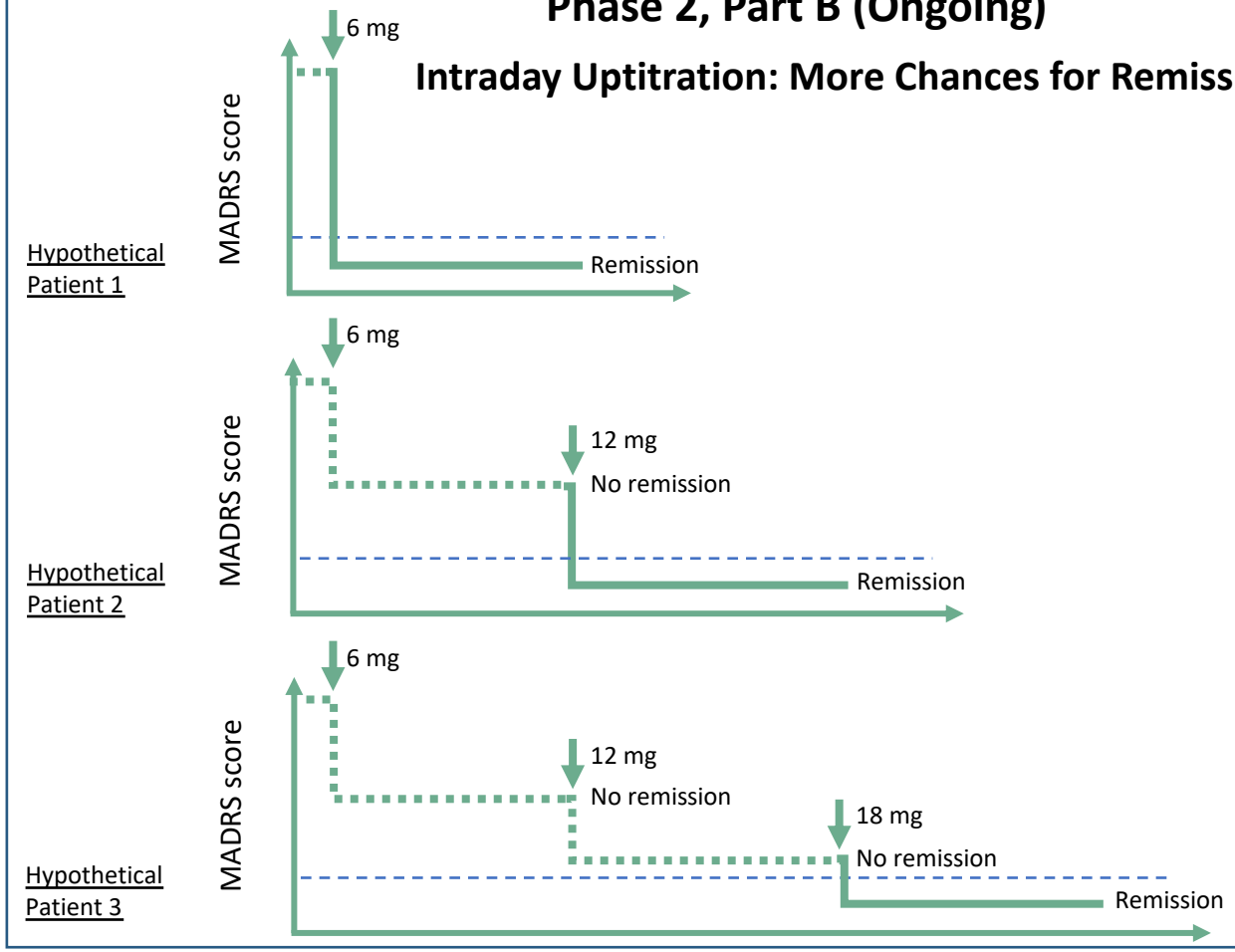
Phase 1, Part A (Completed)

Single dose: 25-50% Remissions Observed[1]



Phase 2, Part B (Ongoing)

Intraday Uptitration: More Chances for Remission



[1]*Range of 25-50% remissions refers to the MADRS remission rate on day 7 for the 12 mg dose group (50%) and the 18 mg dose group (25%) of Part A. The charts on this slide are illustrative and do not reflect actual patient data.*

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

Several patent applications filed:

- Novel aerosol compositions of matter of 5-MeO-DMT
- Novel manufacturing methods of 5-MeO-DMT
- Novel uses of 5-MeO-DMT in various disorders (including inhaled, intranasal, i.v., i.m., s.c., and other routes)

LAYER 3: TECHNICAL

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

GH001

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Anticipated Milestones

- GH001
  - Expected completion of Part B of Phase 1/2 trial in TRD in 4Q 2021
  - Expected completion of Phase 1 clinical pharmacology trial in Healthy Volunteers in 4Q 2021
  - Finalize design of randomized, controlled Phase 2b trial in TRD
  - Initiation of proof-of-concept Phase 2a trials in two new indications
- GH002
  - Complete preclinical work and initiate Phase 1 trial in Healthy Volunteers

Seeking Ultra-Rapid, Durable Remissions in Depression