Expert insights on Huntington's Disease and SOM3355

Webinar

December 10, 2025

DRUG DISCOVERY & DEVELOPMENT

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Webinar Structure

Segment 1 – Huntington's Disease and the patient journey

Segment 2 – Treatment options and medical need

Q&A

Segment 3 – SOM3355 as a potential game changer in the treatment landscape

Segment 4 – Phase 3 pivotal study

Q&A

Closing Remarks

Welcome and Introduction

Daniel Claassen, MD, MS

- Professor of Neurology at Vanderbilt University Medical Center, Nashville, TN (US)
- CEO at Huntington Study Group (HSG)

Victor Sung. MD

- Professor of Neurology,UAB School of Medicine, University of Alabama (US)

Dr. Claassen and Dr. Sung, participated to almost all clinical trials in Huntington disease with symptomatic and disease-modifying treatments.

Silvia Panigone, PhD, MBA

SOM CEO and
Chair of the Board

Rossella Medori MD, PhD

SOM Chief Medical Officer

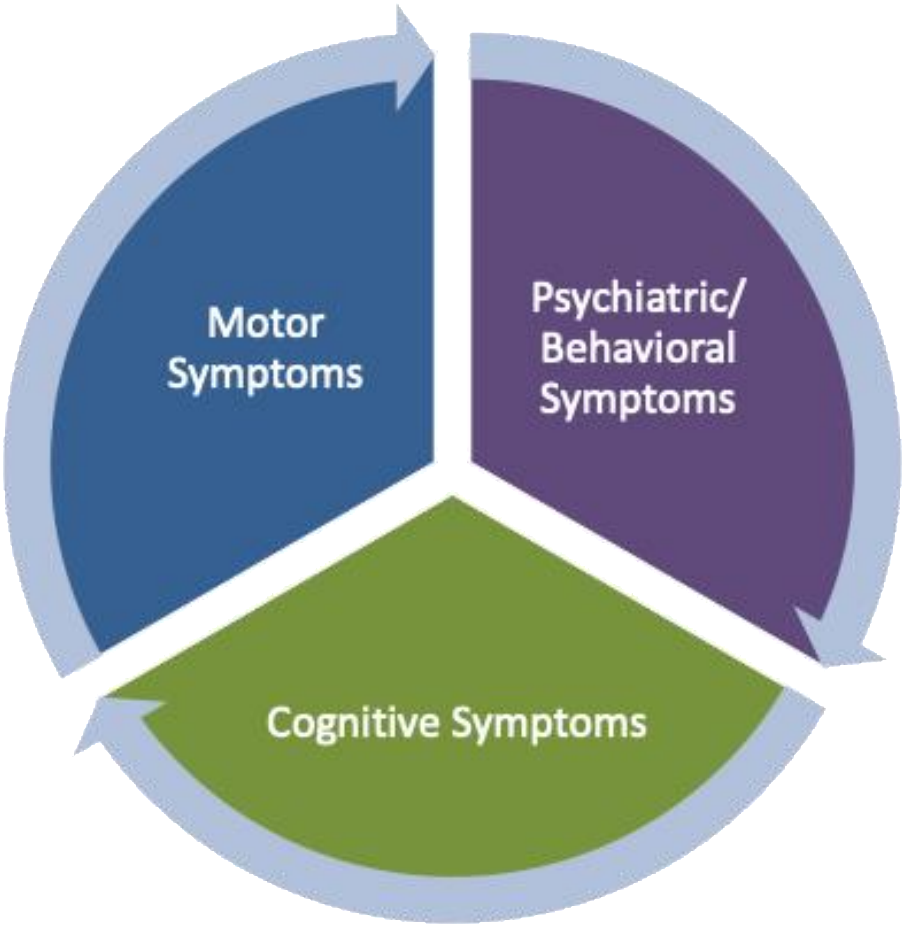
Segment 1
Huntington's Disease and the patient journey

Huntington's Disease

Huntington's Disease and epidemiology

A rare genetic progressive neurodegenerative disease characterized by motor, behavioral and psychiatric symptoms, and cognitive decline evolving until loss of autonomy.

Under-estimated reported prevalence is 5-15 cases per 100'000 and over 250'000 in North America at risk



Cause and age of onset

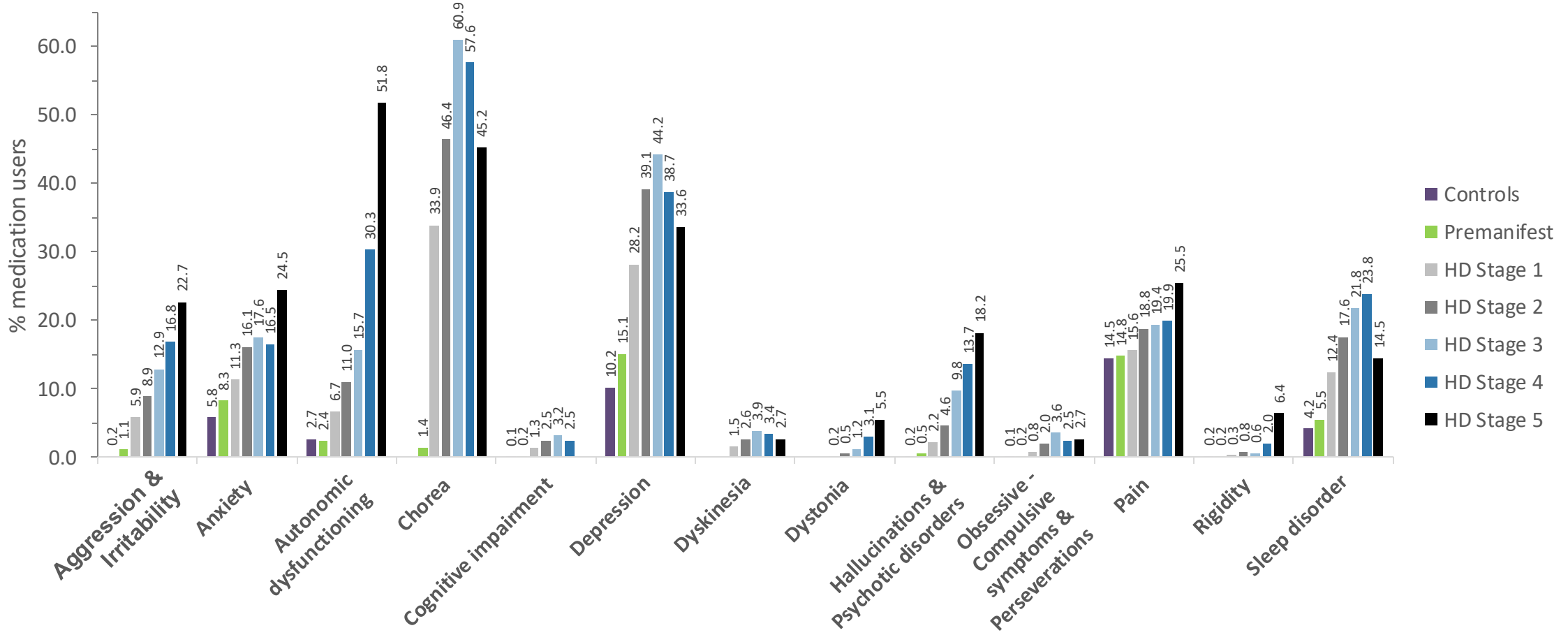
An autosomal dominant mutation in the Huntingtin gene (HTT)
Age of onset - generally around 35-40 years

Diagnosis

Based on family/personal history, neurological examination of movement disorders (chorea, dystonia, UHDRS), psychiatric examination, genetic positive DNA test

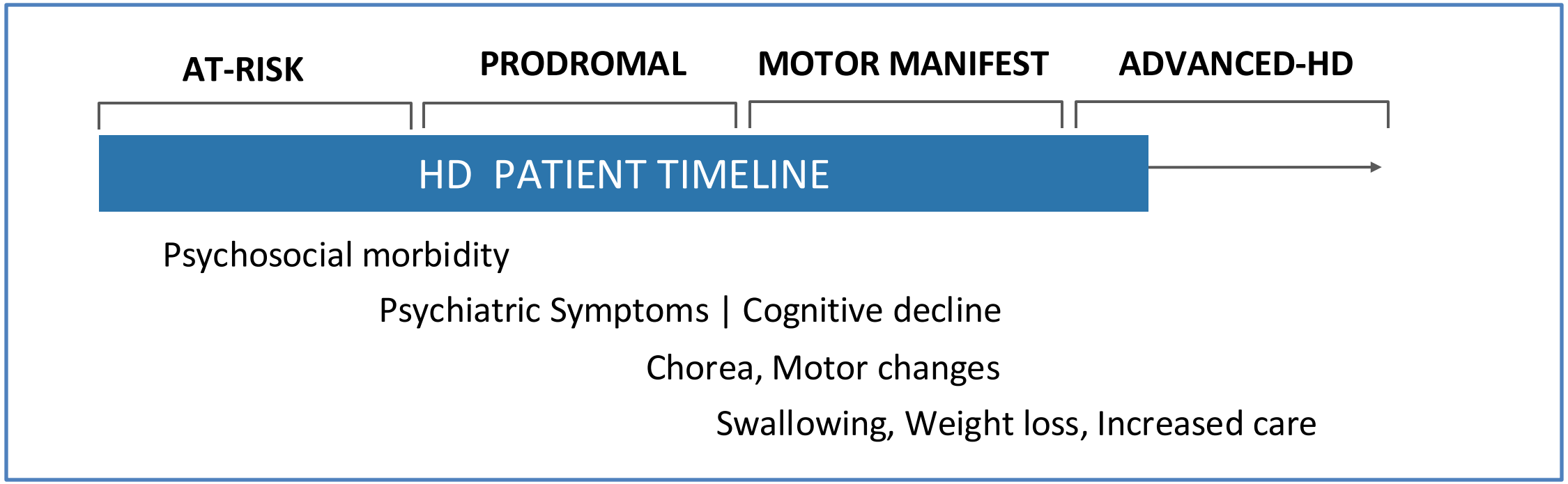
Huntington's Complex Symptomatology Across the Disease Stages

Most often reported HD-related indications per disease group in adult subjects



Source: Feleus 2024 Data from the largest observational HD study, ENROLL-HD

Disease Progression and Patient Journey



- All patients require coordinated multidisciplinary care throughout the course of disease
- **Patients Referral**:

  - 30-40% are self referred to CoE; remain at their primary doctor for long time.

  - when come to CoE, patients often believe to be early symptomatic while they are already at moderate stage

Segment 2
Treatment options and medical need

Currently Approved Treatments

In the US, only 20-30%* HD patients are under pharmacological treatments

Approved Therapies

- FDA approved therapies are solely for chorea
- Approved therapies are VMAT2 Inhibitors, dopamine depleting agents:
  - Tetrabenazine
  - Deutetrabenazine (Austedo®)
  - Valbenazine (Ingrezza®)
- Antipsychotics are used off-label to treat the behavior and neuropsychiatric symptoms

Limitations

- Side effects cannot be distinguished from disease progression (akatasia, depression, parkinsonism, somnolence)
- All approved drugs have Black Box Warning for suicidality and depression
- Titration to adjust the dose
- No approved treatments for behavior and neuropsychiatric symptomatology or cognitive decline

*** Sources:**

1) Longitudinal Treatment Patterns of Chorea in North American Patients with Huntington's Disease: Data from Enroll-HD; Stimming; Neuro Ther Dec 2024
2) Alira Health Analysis – Primary Market Research (KOL N=5, PAG N=2, Payer N=5) committed by SOM

The US Situation - Patient Distribution Across Current Treatments

Out of the **20-30% patients** treated

Center of Excellence
retain **25-30%** the total HD

Xenazine (tetrabenazine) generic — 1-2%
- Rarely used due to AEs
- Used only when required as step therapy

Austedo (deutetrabenazine) — 60-96%
- Perceived **better safety profile**
- Effective **patients support program** by Teva

INGREZZA (valbenazine) capsules — 3-15%
- Not preferred due to **higher sedation rates and limited dosing flexibility**

Off-label neuroleptics — 20-30% *Mono-therapy*; 5-15% *Dual therapy*
- *Consistent across both settings*

Private Practice Neurologist
treat **70-75%** the total HD

Xenazine (tetrabenazine) generic — 40%
- Mostly used as **step therapy or due to cost concerns** for patients unable to afford co-pays for branded products

Austedo (deutetrabenazine) — 35-45%
- Used slightly less than Ingrezza due to the **perception of complicated titration**

INGREZZA (valbenazine) capsules — 25-60%
- Increased use due to **simpler titration regimen,** despite lack of flexibility compared with Austedo

Off-label neuroleptics — 20-30% *Mono-therapy*; 5-15% *Dual therapy*
- *Consistent across both settings*

VMAT2 are the first line when chorea symptoms occur first

Viceversa neuroleptics are the first line when neuro-psychiatric symptomatology occurs first

(1) Alira Health Analysis – Primary Market Research (KOL N=5, PAG N=2, Payer N=5) committed by SOM

Under Development Therapies and Unmet need for HD Treatment

- Under development gene therapy & disease modifying approaches:
  - Slowing down disease progression, prolonging patients' life
  - Pre-symptomatic and early symptomatic patients

- Still a massive need for a chronic treatment of symptoms, even more if disease slows down its progression

- Emerging trends and increased interest for:
  - **non-dopamine depletion agents**
  - **replacement of antipsychotics**

Q&A

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Segment 3
SOM3355 as a potential game changer in the treatment landscape

SOM3355 Molecule - Highlights

- **SOM3355 is a specific beta-blocker used safely as a mild anti-hypertensive for 40 years, currently on the market only in Japan, South Korea and China.**
- **SOM discovered its multimodal MoA: selective beta1-blocker, VMAT1 and VMAT2 inhibitor making it a different class of molecule for the symptomatic treatment of Huntington's Disease (HD).**
- **It has achieved positive results in both proof-of-concept and phase 2b clinical studies in Huntington's patients and showed efficacy and tolerability for the treatment of symptoms behond chorea including behavioural and neuropsychiatric ones, with a very safe profile.**
- **Received positive feedback from both EMA and FDA corroborating the positioning as symptomatic treatment of Huntington's disease beyond chorea.**
- **SOM is committed to move forward with a Phase 3 pivotal study.**

SOM3355: a Unique Novel Mechanism of Action - Differentiation Thesis

Beta Adrenergic Properties

- β-1-adrenergic blockers used to treat akathisia and anxiety
- Long-term use of β-Blocker in HD reported to delay onset and progression of Huntington
- SOM3355 unique action among β-Blocker

Positive impact on akathisia and anxiety; potentially contributing to delay progression of HD

VMAT2 Inhibition With Dopamine Modulation

- Binding to VMAT2 in a different binding side then tetrabenazine (TBZ) with similar inhibition potency of TBZ
- 10-fold less potent than TBZ in inhibiting serotonin (5HT) uptake

Lack of the side effects caused by dopamine depletion (depression, parkinsonism, fatigue)

VMAT1 Inhibition

- Bind to VMAT1 with same potency as VMAT2
- Located in the CNS, in other regions of VMAT2
- Linked to the emotional brain circuits. A few antipsychotics inhibit VMAT1 (eg. Ziprasidone)

Possible antipsychotic and antianxiety effects and limitation of dopamin depletion side effects

Efficacy

- In the Phase 2b double blinded, 12-weeks, placebo-controlled study, 140 pts with 2 doses, **SOM3355 300mg BID** (the highest dose) **showed statistically significant reduction in the TMC scores** compared to placebo (p=0.04) at endpoint with reductions from baseline that reached -4.73, similar to changes reported by marketed drugs
- The Clinician and Patient global impressions of change (**CGI-C and PGI-C) showed significantly higher percentage of patients improved for SOM3355 300mg BID compared to placebo**
- **Improvement was also seen in Anxiety, Apathy, Compulsive, Disruptive and Irritable behaviors and Perseverative Thinking** by Problem Behaviors Assessment (PBA-s) in HD patients who had these disturbances, although mild, at baseline while some of them showed mild worsening on placebo

Safety

- **At Beck Depression Inventory (BDI) - No case of worsening of depression**. **Depressive symptoms improved** in the 300mg BID SOM3355 group with mild depression at baseline
- **No** increased suicidality at Columbia-Suicide Severity Rating Scale (C-SSRS) on Drug . Of 21 patients with history of suicidality at screening or baseline, only three patients reported suicidality during the study and they were all in the placebo group
- **No** somnolence according to the Epworth Sleepiness scale (ESS) was reported, on the contrary, improvement in the daytime sleepiness was observed in some cases
- **No** akathisia according to Barnes Akathisia Scale was reported in all treatment groups
- **No** changes in cognitive function according to MoCA
- **No** fatigue or falls compared to placebo

Safety and Cardiovascular Safety

Related Treatment Emergent Adverse Events of special interest (related and possibly related)

- Bradycardia : 2 cases in 200 mg BID and 6 cases in 300 mg BID group
- Syncope : 1 case in each of the 3 treatment groups
- Hypotension : 1 case in 200mg BID and 1 in 300mg BID group
- Suicidal ideation : 1 case in Placebo group (SAE)
- Delusion worsening requiring neuroleptic: 1 case in 300mg BID assessed as not related by the investigator

Heart rate - expected, dose-related decrease in heart rate within the normal range and return to baseline after discontinuation. More importantly, **a plateau effect** was reached with 200 mg BID.

No effect on QT prolongation

No dose adjustment needed

Experts Opinion – SOM3355 as a Potential Game Changer in the Treatment Landscape

- What is catching your attention on SOM3355?
- For which patients would you use it, if the profile is confirmed in Phase 3?

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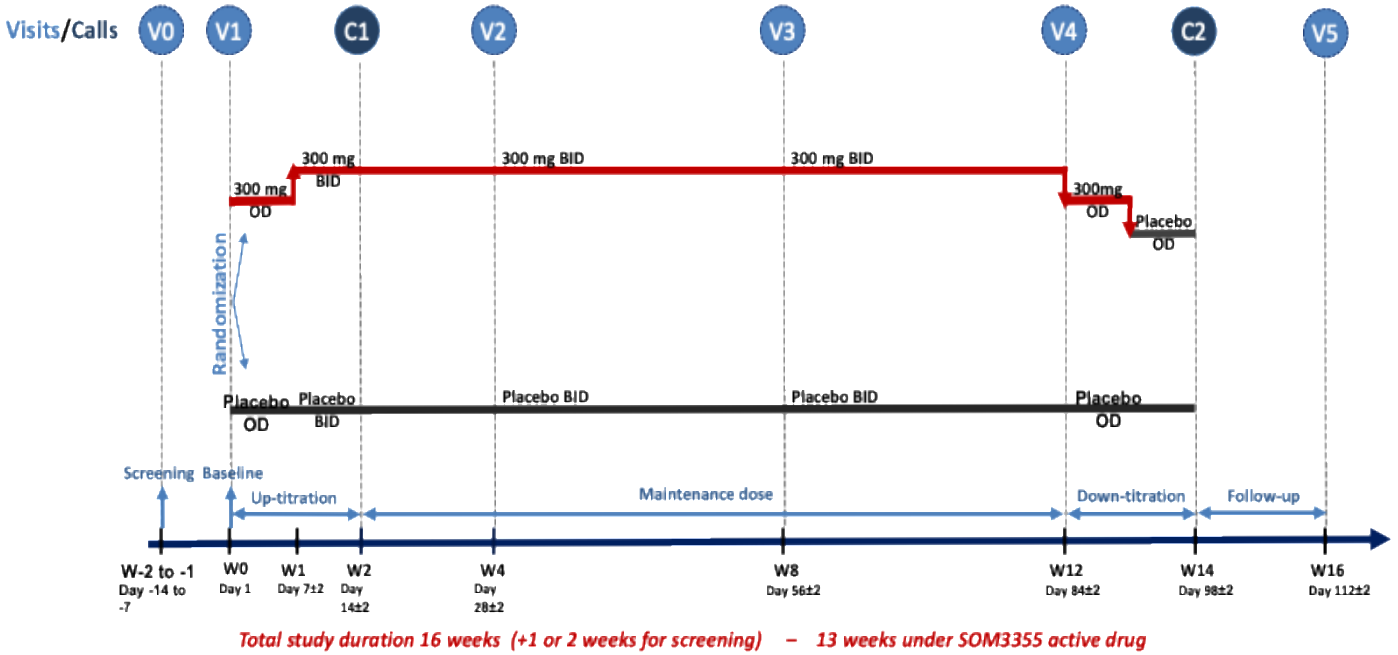
Segment 4
Phase 3 Pivotal Study

Phase 3 Pivotal Study

- End-of-Phase 2 meeting with FDA defined a clear registrational path
- One pivotal study
- 12-weeks placebo controlled, one dose (300mg BID), double blinded with less than 120 evaluable patients to drive to approval
- Followed by Open Label Extension up to 9 months



- Protocol under final drafting:
  - replication of endpoints to confirm Phase 2 safety & efficacy data
  - incorporation of additional efficacy endpoints, as recommended by regulators, to more characterize the drug's clinical potential
- Planned to start by end 2026

Experts Opinion – Phase 3 Pivotal Study

- Given what we just reviewed as the potential final protocol, which endpoints - if demonstrated – would most strengthen your belief that SOM3355 could be considered the drug of choice for the symptomatic treatment of Huntington patients?
- How comfortable are you with this study design in terms of recruitment and study completion?

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Thank you for your attendance

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