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SOM3355: Chorea movements associated with Huntington's disease

SOM BIOTECH

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Imagine a FUTURE where you can

Rescue your failed drugs

Build your own pipeline

Put your R&D process on the new level

In any therapeutic area and indication

With small/medium molecules (<1,200 Da)

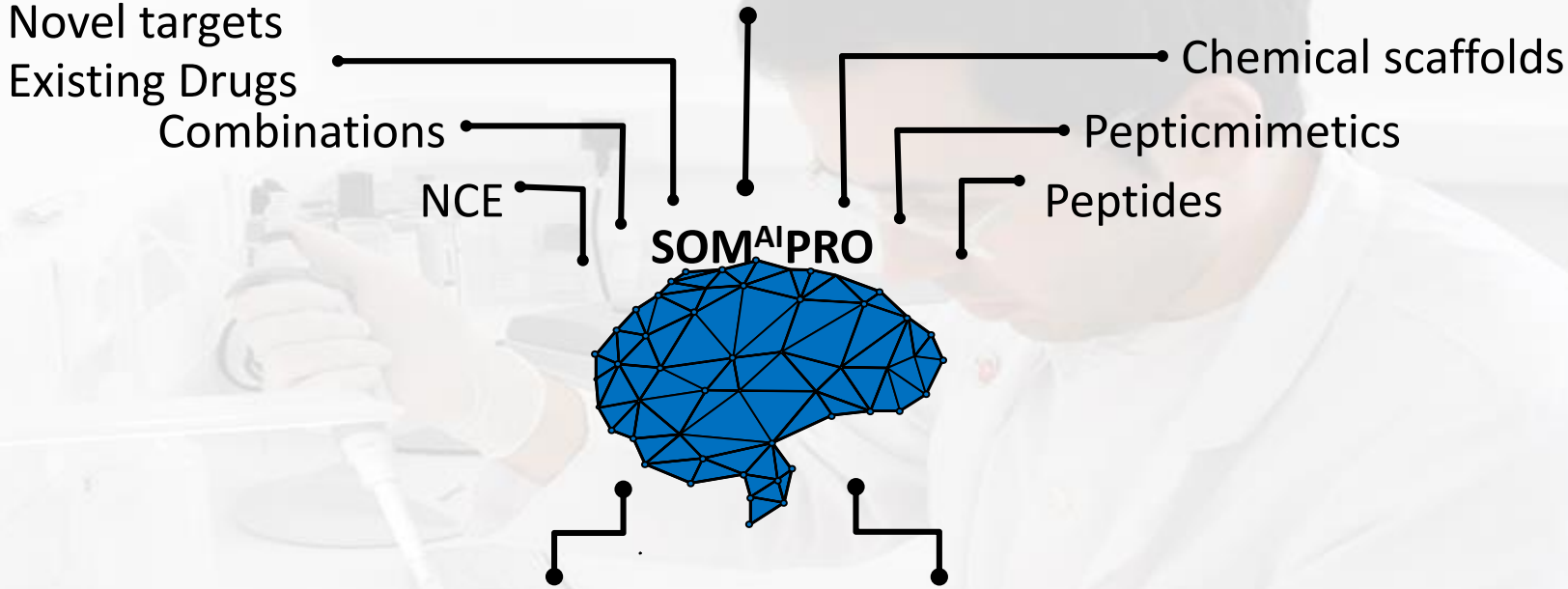
Securing WW Patent & Market protection

TIME	COST	RISK
Reduced* x 3	Reduced* x 40	Reduced* x 10

* In repurposed drugs

At SOM Biotech we already achieved that

Pipeline building and extension for new MoA and indications



Applying the technology, we:

- Built a **robust portfolio, mainly focused on Orphan CNS diseases,** containing **7 products in development** and **20 in drug discovery.**
- **Two of our programs successfully completed Phase 2a** (combined potential peak sales of more than €2.8bn).
  - Our **COVID-19 program** was developed into Phase 2a in just four months.
  - Achieved **two out-licensing** agreements; **12 International patents** were filed**.**

SOM3355: Target Indication. Chorea in Huntington's disease.

Chorea:

- Involuntary movements characteristic of Huntington's disease (HD)[1].

- Symptoms appear between 30 to 50 years old and get worse over a 10 to 25-year period[2].

Diagnosis:

Generally based on genetic testing, findings from neurological, and psychological testing.

Disease management:

There are 50 Centres of Excellence in US[2]. In EU there are more than 230 clinics[3].

Management of symptoms:

Neurologists, psychiatrists and speech pathologists[2].

Chorea symptoms

- Debilitating problems in the swallowing and the production of speech. Involuntary jerking.
- Muscle problems: rigidity or muscle contracture.
- Slow or abnormal eye movements.
- Impaired gait, posture and balance.

Chorea interferes with activities of daily living; it is socially isolating.

Mortality

- **Life expectancy** with HD is normally **15-20 years** from the onset of symptoms[1].
- People with HD die of other **life-threatening complications** related to the disease; **heart** disease and **pneumonia** are the leading causes of death[1].

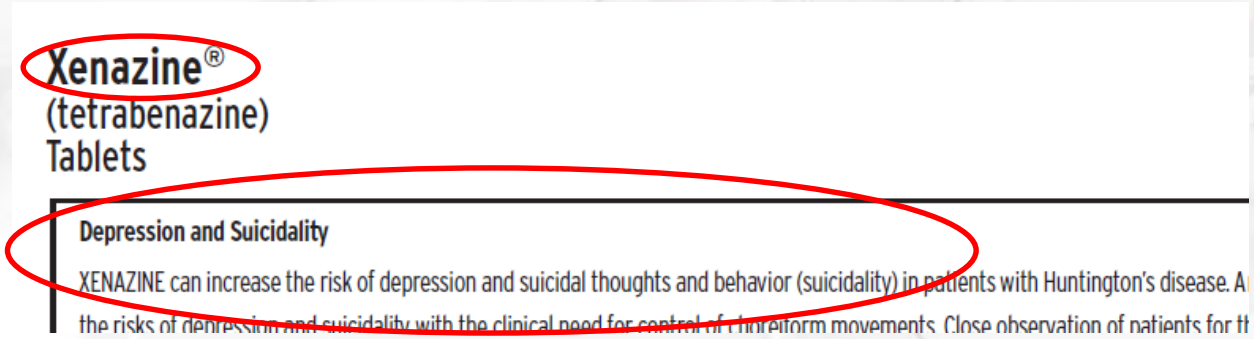
1.Huntington's Disease Information Page: National Institute of Neurological Disorders and Stroke (NINDS). Retrieved on the 5th of March 2020.
2. Huntington's Disease Society of America Page. Retrieved on the 5th of March 2020. 3. European Huntington's Disease Network. Retrieved on the 4th of March 2020.

SOM3355: Differential features. Unmet need: SAFETY.

XENAZINE and AUSTEDO have a BLACK BOX: <u>INCREASE</u> DEPRESSION AND SUICIDALITY

Xenazine (Tetrabenazine)
MoA: VMAT2 inhibitor
Company: Bausch Health Companies, Lundbeck.
Price patient/year in US: $150,000.
(Generics are available at 1/10th of this price).
Market: Marketed WW.

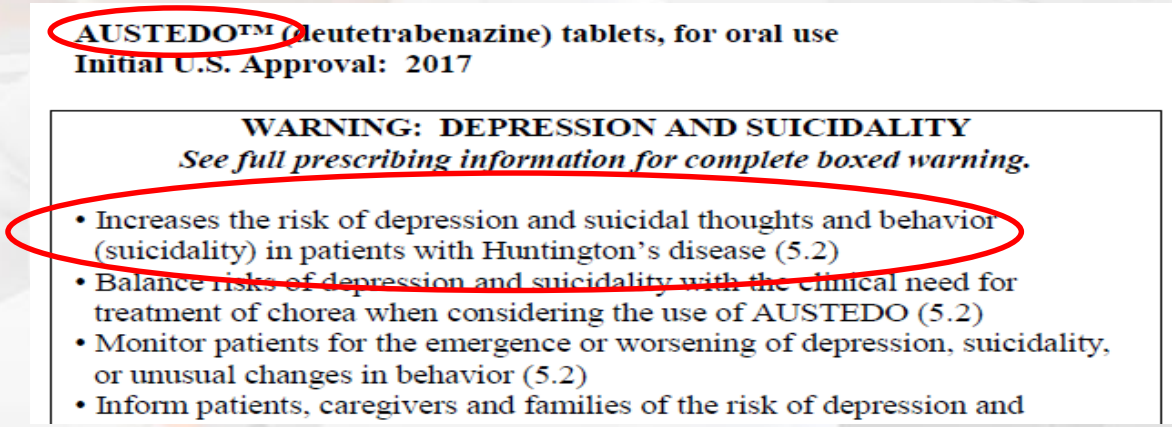
Austedo (Deutetrabenazine)
MoA: VMAT2 inhibitor
Company: Teva Pharmaceutical Industries.
Price patient/year in US: $48,000.
Market: Marketed in the US.
Sales for 8 years: $18.9B (peak sales $1.4B).



Xenazine®
(tetrabenazine)
Tablets

Depression and Suicidality

XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. A
the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation of patients for th



AUSTEDO™ (deutetrabenazine) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DEPRESSION AND SUICIDALITY
See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO (5.2)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
- Inform patients, caregivers and families of the risk of depression and

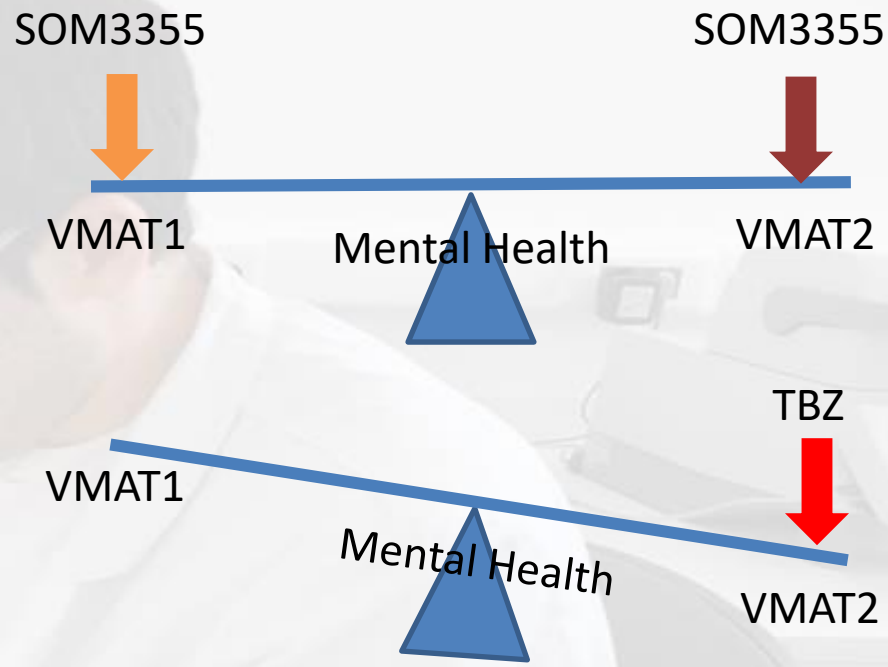
≈60% OF PATIENTS WITH HUNTINGTON'S DISEASE SUFFER FROM DEPRESSION[4].
SUICIDE IS A CAUSE OF DEATH IN 8–9 % OF DE PATIENTS[5] .

48,041 : Target population of SOM3355 in EU5 and US *

4 . The psychiatric phenotype in Huntington's disease. Jennifer Charlotte de Souza. University of Birmingham, 2015.
5. Treatment of Huntington's Disease. Samuel Frank. Neurotherapeutics. 2014 Jan; 11(1): 153–160. Published online 2013 Dec 24.
* Patients diagnosed with Huntington's disease according to GlobalData.

SOM3355: Innovative mechanism of action

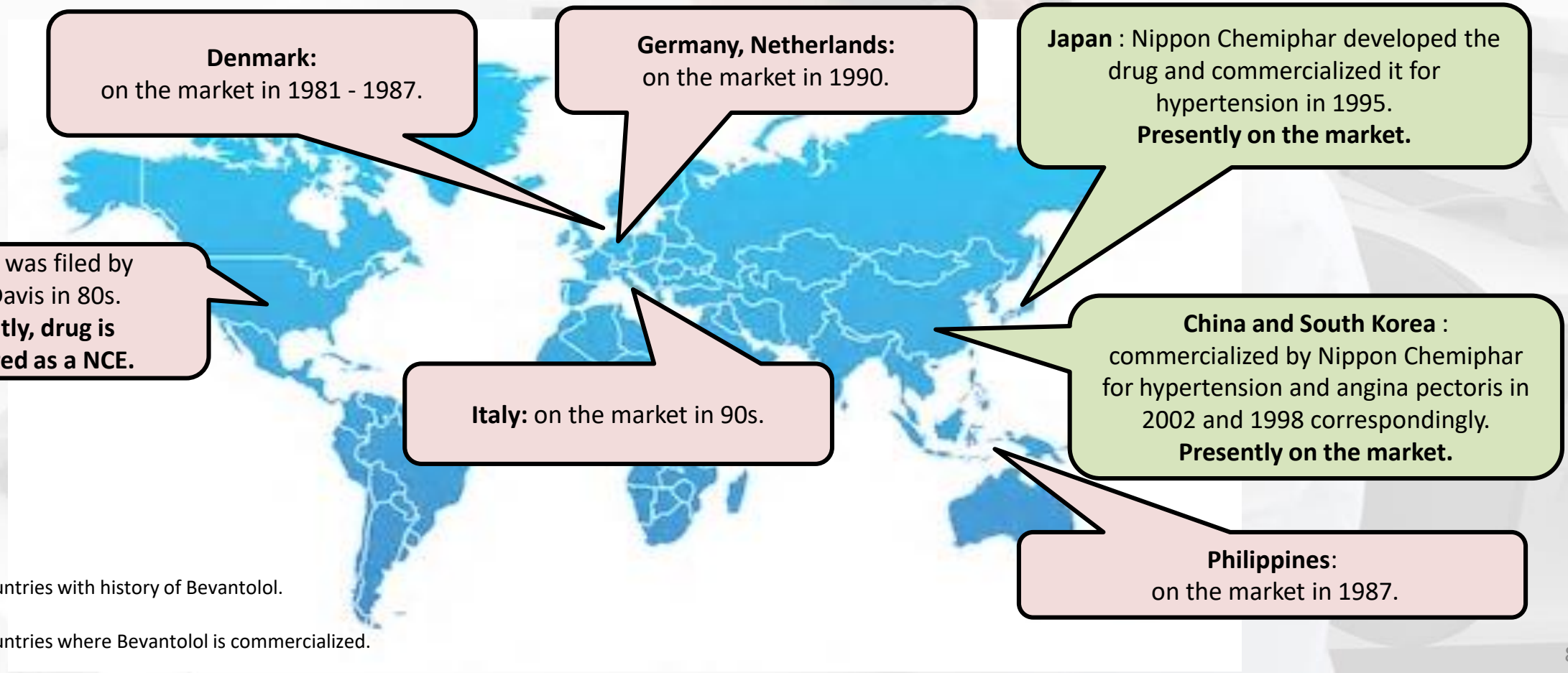
	SOM3355	TBZ	Conclusion
Functional VMAT2 inhibition (IC50 nM)	98	75	SOM3355 equipotent to TBZ in functional VMAT2 inhibition
Binding to TBZ site on VMAT2 (Ki nM)	1900	51	SOM3355 binds to another site on VMAT2 or interacts with same site in different way
Functional VMAT1 inhibition (IC50 nM)	44	>20000	SOM3355 inhibits VMAT1, TBZ does not



SOM3355 differentiates from Tetrabenazine in interaction with VMAT2 and inhibition of VMAT1 which provides a balanced change in monoamine signalling ameliorating the motor symptoms of HD but preserving mental well-being

SOM3355: Regulatory map

Bevantolol (VMAT2 inhibitor) was discovered by Parke-Davis (US) and licensed to Nicomed (EU) and Nippon Chemiphar (JPN).
Priority patent for Bevantolol (US 1971-207954) has already expired. In **US** it is considered a **New Chemical Entity.**
Approved dosage in Europe: up to 400 mg/day.
Clinical data: in 420 US and EU patients and in 900 Japanese patients + pharmacovigilance data since approval 1995.

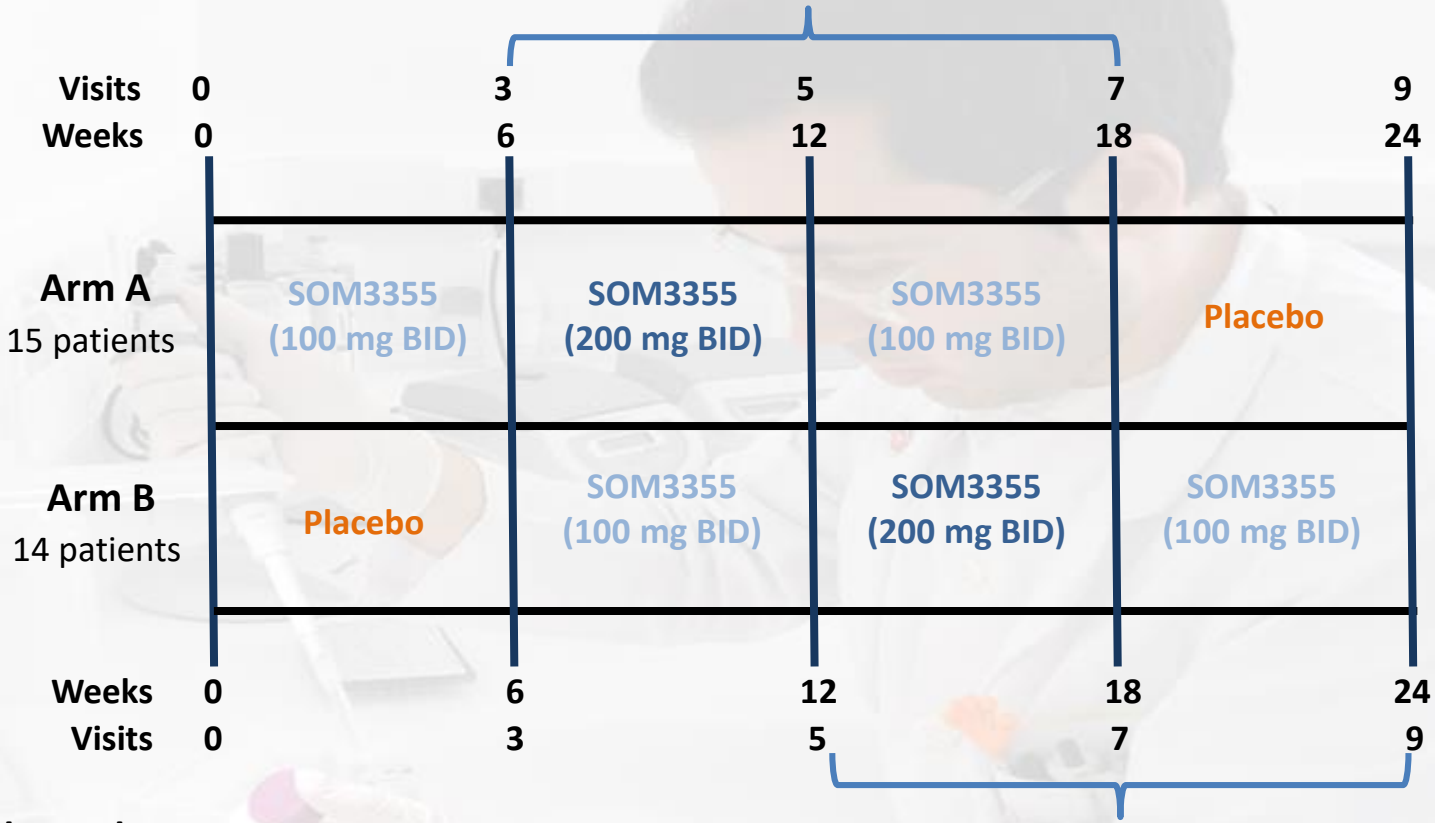


Current status: Phase 2a POC positive results obtained

Primary End Point:
Improvement in any active drug period in TMC score of at least 2 points compared with placebo period. We were looking to the responder rate.

Total Maximal Chorea score (TMC):
this is a 28 score rating system to quantify the severity of Chorea in Huntington's Disease.

Arm A:
Endpoints at end of each period (6th week) compared to TMC score at V9 (end of placebo period)



Arm B:
Endpoints at end of each period (6th week) compared to TMC score at V3 (end of placebo period)

Four sites in Spain

CLÍNIC BARCELONA Hospital Universitari

Bellvitge Hospital – Institut Català de la Salut

Hospital de la Santa Creu i Sant Pau – Universitat Autònoma de Barcelona

Vall d'Hebron Hospital

The Phase 2a results showed:
TMC improvement ≥2 points versus baseline:
76% under SOM3355 and
41% under placebo (p=0.0156).
The highest SOM3355 dosage was statistically significant.

Phase 2b/3 is under development: applications for Pre-IND with FDA and Scientific advice with EMA were submitted.
More data are available under CDA.

SOM3355: IP and Orphan Drug designation

Strengths of the market protection and regulatory development

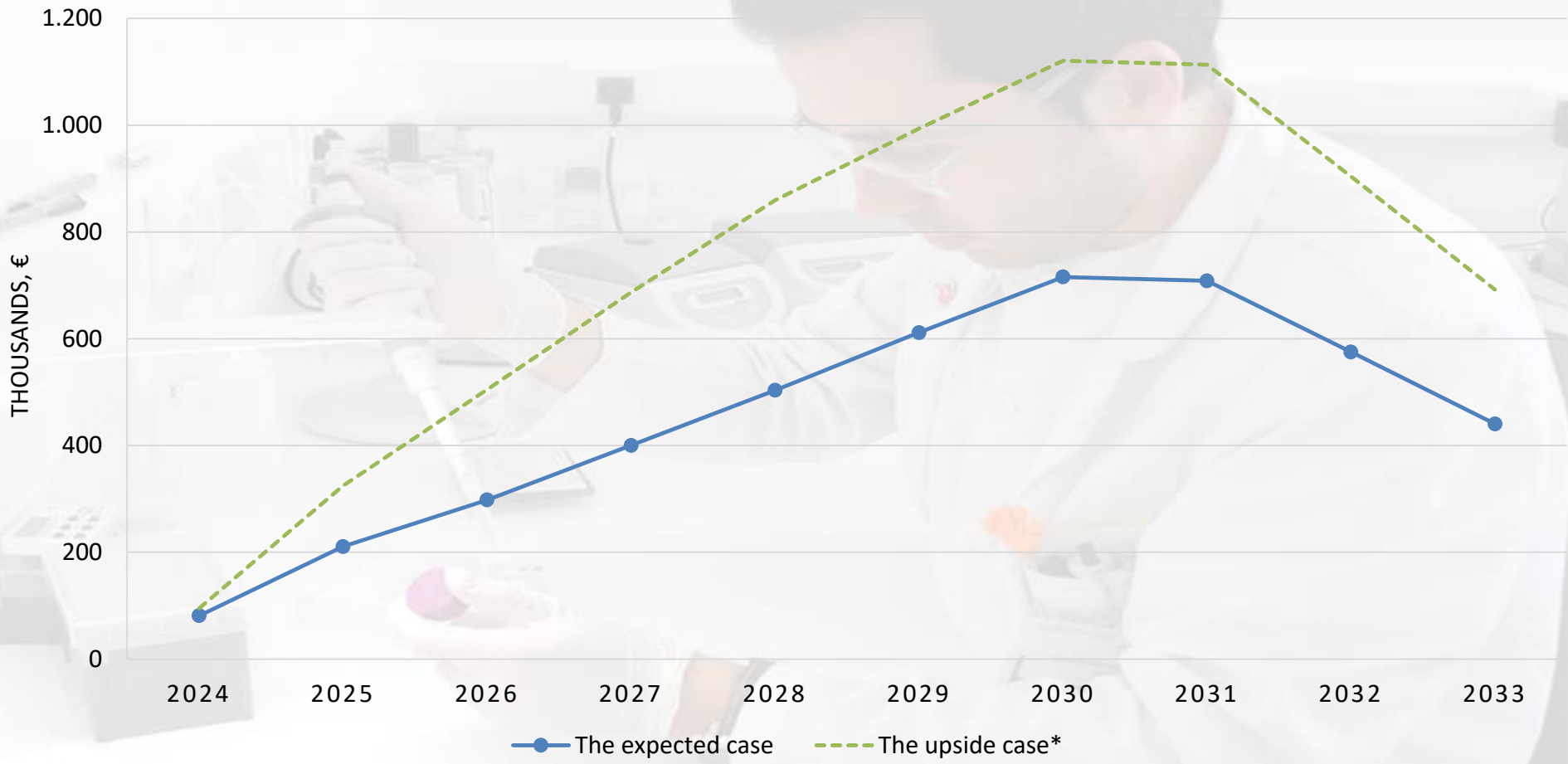
- **US:** The drug is considered as a NCE.
- **Orphan Drug Designation:** ongoing. Market exclusivity period of 7-10 years will be guaranteed. Possible Fast Track Designation.
- **Patent includes:** racemic mixture, enantiomers and combinations.
- **Bevantolol is commercialized in:** China, Japan and South Korea.

Patent of a new use of Bevantolol

- **PCT Patent publication on 24th Dec 2014**
  Publication number: WO 2014/202646 A1.
- **National Stage entry in Dec 2015**
  US, Euro-PCT, Japan, Hong Kong, Australia, Brazil, Canada, Chile, China, South Korea, Israel, Mexico, New Zealand, Singapore, South Africa and Russia.
- **Granted**: Australia, China, Russia, Japan, Singapur, Mexico, Israel, US.

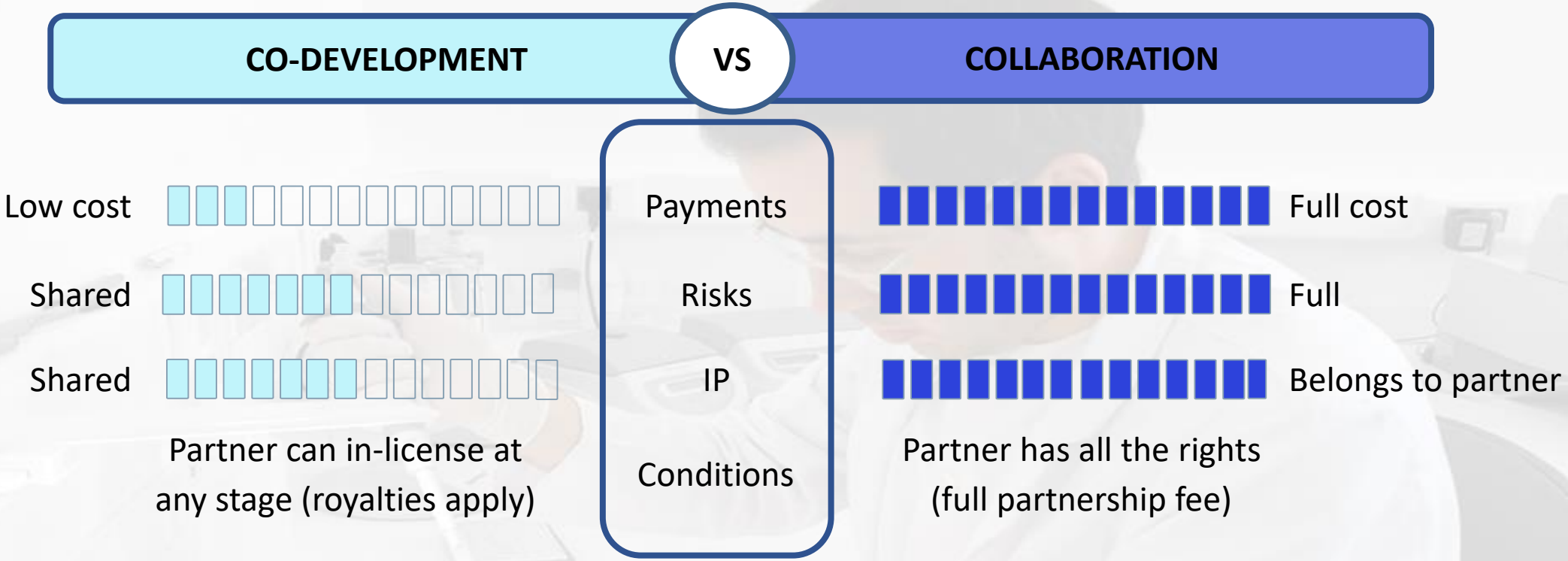
SOM3355: Estimated sales

Estimated sales in 2024 – 2033: €700M – €1.120M ww.



* The upside curve is driven by the lack of psychiatric adverse effects observed in clinical trial and pharmacovigilance data of SOM3355.

Partnering opportunities



SOM Biotech is open to a broad type of business agreement, starting from co-development or out-licensing of our **assets** to partnership for a **SOM^{AI}PRO technology.**

The collaboration type based on a SOM^{AI}PRO technology ultimately will depend on the therapeutic indications, a number of projects, territory, and level of drug development achieved.

SOM3355: Conclusions & Risks

- **Positive Phase 2a proof of concept trial in Huntington patients (n=32).**

  ⇨ **provides the confirmation of the expected effects of SOM3355 on the chorea symptoms** related to VMAT2 inhibition.

  ⇨ **Excellent safety profile particularly regarding to** known side effects of Xenazine and Austedo.

  no suicidality, no depression induced and no concern about QT prolongation.

- **Known safety profile of Bevantolol with large experience in hypertensive patients with doses up to 800 mg/day.**

  allowing to test higher doses to get a stronger effect.

- **Eligible for Orphan Drug Designation and considered as a NCE in the US.**

  never registered in the US ⇨ 5-year NCE exclusivity.
  orphan drug designation ⇨ 7-year exclusivity in USA, 10-year exclusivity in EU.

- **Opportunity of an enantiomer development:** more potent and safe.
- **Peak sales estimation** for Huntington Disease : €700M – €1.120M ww.
- Potential opportunity for an extension of indication in **Tardive dyskinesia** (similar MoA) with peak sales of €600M ww.
- **Patent** of use already granted in many countries (US included).
- **Risks:** It may take longer time for the enantiomer development and extension of indication in Tardive dyskinesia.

Would you like to know more?

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