Proof-of-concept study testing bevantolol (SOM3355) as treatment of chorea in Huntington's disease

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Objective

Proof-of-concept phase IIa study assessing bevantolol (SOM3355) efficacy and safety in reducing chorea in Huntington's disease (HD).

Background

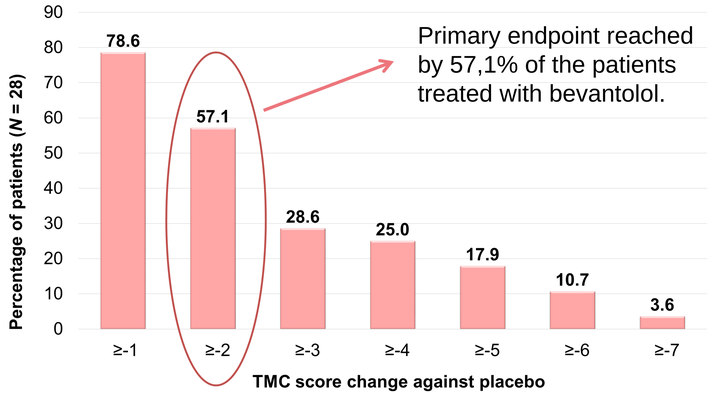
SOM^{AI}PRO
- Artificial intelligence screening to repurpose known drugs.
- Identification of bevantolol hydrochloride as a potential Vesicular Monoamine Transporter type 2 (VMAT2) inhibitor.

Preclinical
- VMAT2 inhibition confirmed by *in vitro* functional studies.
- Brain penetration confirmed by *in vivo* studies.

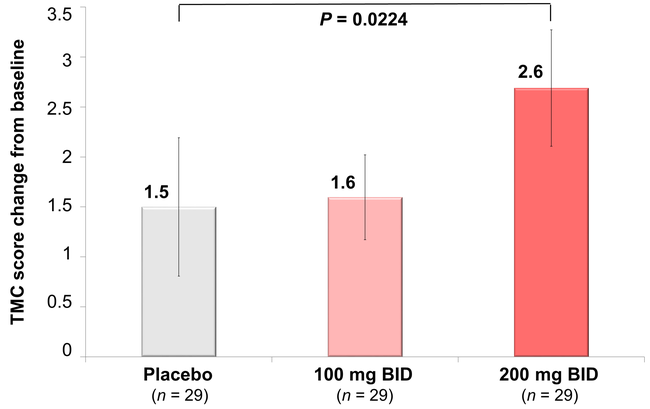
Phase IIa
- Proof-of-concept study to assess whether bevantolol safely reduces chorea in patients with Huntington's disease.

Primary endpoint

Primary efficacy endpoint: improvement ≥ 2 points in the total maximal chorea (TMC) score of the Unified Huntington's Disease Rating Scale (UHDRS) in any active drug period compared with the placebo period.

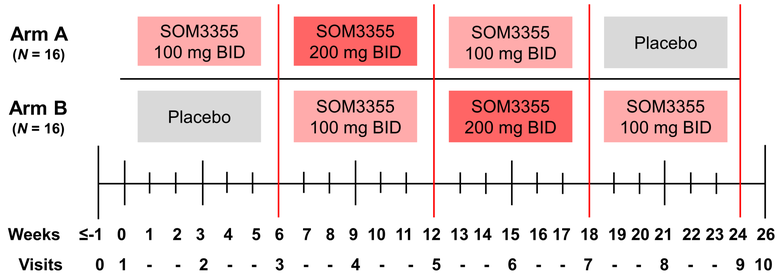


Mixed-model analysis comparing the different periods showed significant improvement in the TMC score with bevantolol 200 mg BID vs placebo.



Methods

Double-blind, randomized, crossover, placebo-controlled study in 32 patients.



Secondary Endpoints

- CGIC and PGIC scales showed improvement in more than 72% of patients.
- Bevantolol was well tolerated with only mild or moderate adverse events.
- Most frequent treatment emergent adverse events were bradycardia (*n* = 5), fall (*n* = 5), hypotension (*n* = 4) and insomnia (*n* = 4).
- A dose-proportional reduction of the pulse rate and blood pressure, albeit within normal ranges, was recorded during the periods under bevantolol and is consistent with the β1-adrenoceptor antagonist effects of the drug.
- No AEs of depression or suicide were reported during the treatment periods.
- No deaths, no SUSARs, and only one SAE (hospitalization for delirium, unrelated to the study treatment, and under placebo) were reported.

Exploratory Endpoint

- Bevantolol induced a mild increase in mean (SD) prolactin plasma levels ($P < 0.005$), consistent with the profile of VMAT2 inhibition.

Placebo (*n* = 27)	100 mg BID (*n* = 28)	200 mg BID (*n* = 28)
14.5 (17.0)	25.6 (25.2)	28.8 (32.9)

Conclusion

This study confirms that bevantolol reduces chorea in patients with Huntington's disease and has a good safety profile.