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BRIGHT MINDS

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A phase 1 clinical study of BMB-101 shows linear PK and a reduced rate of somnolescense and GI/Urinary side effects compared to other 5-HT$_{2C}$ agonists

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Background

The 5-HT$_{2C}$ receptor, a subtype of the serotonin (5-hydroxytryptamine, 5-HT) receptor family, plays a pivotal role in various neurological and psychiatric processes, and agonists are promising candidates for therapeutic intervention. Recently, 5-HT$_{2C}$ agonists demonstrated strong efficacy in Developmental and Epileptic Encephalopathies (DEE) disorders.

Somnolence/lethargy and gastrointestinal (GI)/Urinary side effects are commonly seen with 5-HT$_{2C}$ agonists (fenfluramine, lorcaserin, and bexicaserin) used for the treatment of DEE. These side effects can significantly impact patients' quality of life and lead to drug discontinuation. In recent studies BMB-101 demonstrated a reduced rate of somnolence and GI/Urinary side effects compared to other agents in this class. The purpose of this analysis was to explore the relationship between the pharmacokinetic and pharmacodynamic (PK/PD) profiles of 5-HT$_{2C}$ agonists and side effects.

Study Design

This was a randomized, double-blind, placebo-controlled Phase 1 study of BMB-101 in healthy volunteers.

Single Ascending Dose:

Eligible participants were assigned to 1 of 4 ascending dose cohorts, 8 per cohort (6 active, 2 placebo).

- 20 mg/70 kg
- 60 mg/70 kg
- 120 mg/70 kg
- 180 mg/70 kg

Multiple Ascending Dose (MAD):

Eligible participants were assigned to 1 of 4 ascending dose cohorts, 8 per cohort (6 active, 2 placebo). Study drug was administered twice daily (BID) for 7 days, 12 hours apart, with only the morning dose on Day 7.

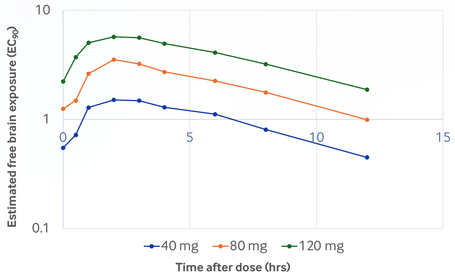
- 40 mg/70 kg
- 80 mg/70 kg
- 120 mg/70 kg
- 150 mg/70 kg

Pharmacokinetics

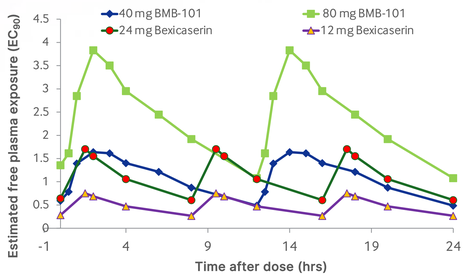
BMB-101 demonstrated dose linearity in the dose range of 40-120 mg BID which was explored in the Phase 1 MAD study. The maximum tolerated dose (MTD) was considered 150 mg.

- Steady-state PK/PD modeling of BMB-101 and bexicaserin showed that BMB-101 40 mg BID had an identical target occupancy profile compared to bexicaserin 12 mg three times daily (TID), with identical C_{max}/C_{ave} and C_{trough} values over a 24-hour period
- Doubling the BMB-101 dose from 40 mg BID to 80 mg BID dramatically increased the brain target occupancy for BMB-101 to 2.5 x the 90% effective concentration (EC_{90}) with no increase in undesirable side effects

Estimated free brain exposure EC_{90} of BMB-101



Comparative free plasma exposure over estimated EC_{90} of BMB-101 BID vs bexicaserin TID



Safety

- Somnolence/lethargy are frequent adverse events (AEs) in trials of antiseizure medications, impairing daily functioning, reduce quality of life, and leading to patient discontinuation of effective therapies
- The rates of somnolence/lethargy and gastrointestinal (GI) side effects were notably lower in Phase 1 trials of BMB-101 compared to fenfluramine and bexicaserin
- The therapeutic dose of BMB-101 is 40 to 80 mg BID for a 70 kg adult. Over 60% of the AEs were observed at the MTD of 150 mg BID and were transient.

Effects of 5-HT$_{2C}$ Agonists on Somnolence/Lethargy, Gastrointestinal, and Urinary Side Effects

	Bexicaserin MAD Phase 1[2]	Bexicaserin Phase 1b/2a[3]	Fenfluramine 0.2 mg/kg/day Phase 3 in DS[4]	Fenfluramine 0.7 mg/kg/day Phase 3 in DS[4]	Fenfluramine open-label trial for CDD[5]	Fenfluramine open-label trial for Sunflower Syndrome[6]	BMB-101 MAD Phase 1[1]
Somnolence Lethargy	36%	28%	11%	21%	86%	0% Fatigue 37%	4% Dizziness 4%
Constipation	20%	14%	Not reported	Not reported	29%	0%	0%
Diarrhea	24%	12%	15%	15%	29%	11%	0%
Other GI	Not reported	Decreased appetite 21%	Decreased appetite 38%	Decreased appetite 26%	Vomiting 14%	Decreased appetite 42%	Oral paresthesia 13% Nausea 8% Decreased appetite 4%
Urinary side effects	Micturition urgency 28%	Urinary tract infection 7%	Not reported	Not reported	Not reported	Nocturnal enuresis 11%	0%

Pharmacodynamics

- Prolactin increase serves as a central PD biomarker for detecting activation of 5-HT$_{2C}$ receptors
- As a binary biomarker, it indicates the threshold dose at which receptor activation occurs. Typically, a 3-fold increase in prolactin release is observed once threshold serotonin levels have been reached.[1]
- BMB-101 60 mg BID is estimated to have steady-state target exposure similar to bexicaserin 12 mg TID

	Threshold dose of prolactin increase	MTD	MTD/dose for receptor activation
Bexicaserin phase 1[1]	12 mg TID	18 mg TID	~1.5
BMB-101 Phase 1	40-80 mg BID	150 mg BID (2.15 mg/kg BID)	~2.5

- Both BMB-101 and bexicaserin are highly selective 5-HT$_{2C}$ agonists with minimal activity at other 5-HT receptors, whereas doses of fenfluramine and lorcaserin are limited by 5-HT$_{2B}$ and 5-HT$_{2A}$ activity
- BMB-101 has no dose-limiting AEs at the projected therapeutic dose range

	MTD	Dose-limiting AEs
BMB-101	2.15 mg/kg BID	Headache
Fenfluramine	0.7 mg/kg/day and 28 mg/day	Dose limitation due to cardiac risks resulting in the need for REMS program with cardiac monitoring
Bexicaserin	18 mg TID	Headache/Somnolence/GI
Lorcaserin	10 mg BID	5-HT$_{2A}$ effects

Conclusions

- In contrast to other clinical stage 5-HT$_{2C}$ agonists, BMB-101 has linear PK in predicted therapeutic doses, ensuring that dose changes result in predictable and proportional changes in drug exposure
- The Phase 1 clinical trial of BMB-101 demonstrated that the improved PK/PD properties compared to those of existing 5-HT$_{2C}$ agonists resulted in a better tolerability profile
  - A decreased incidence of somnolence/lethargy and fewer GI/Urinary side effects were seen with BMB-101 vs. other 5-HT$_{2C}$ agonists
- Based on prolactin activation, selectivity, and safety/tolerability in Phase 1, BMB-101 has an improved therapeutic window
- The linear PK of BMB-101 coupled with its acceptable side effect profile potentially offers a more favorable therapeutic option for patients with epilepsy

References

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