Bright Minds Biosciences Inc. New York, NY, USA
Bright Minds Biosciences Pty Ltd, Carlton South VIC, Australia

2025 AES ANNUAL MEETING
DECEMBER 5-9 • ATLANTA

Safety, Tolerability, and Pharmacokinetics of Novel 5-HT_{2C} Agonist BMB-101 (Phase 1 Clinical Study)

A Vasilkevich[1], A Lovera[1], J. Duan[1], I McDonald[1], J Sourbron[2], MA Smith[1], JT Pedersen[1]

[1]Bright Minds Biosciences Inc. New York, NY, USA; Bright Minds Biosciences Pty Ltd, Carlton South VIC, Australia; [2]Ghent University Hospital, Ghent, Belgium

Background

- **BMB-101 is a novel, highly selective 5-HT_{2C} receptor agonist**
- **Based on the currently available data, BMB-101 is the only compound that has shown to be a "biased" or "functionally selective" 5-HT_{2C} agonist in clinical development**
- **BMB-101 is biased for the Gq signaling pathway with minimal β-arrestin recruitment, which underlies the reduced potential for tolerance**

Highly selective 5-HT2C receptor agonist

- BMB-101 has an absolute EC50 of 16 nM at 5-HT_{2C} receptor
- BMB-101 shows minimal 5-HT_{2A} and 5-HT_{2B} receptor activity without liabilities linked to the psychedelic and cardiotoxic effects, respectively[1,2]
- No significant activity at other serotonin receptors

Biased agonism: Lack of β-arrestin recruitment at 5-HT_{2C}R

- Arrestin activation is related to receptor downregulation, desensitization, and tolerance.[3] This effect was seen for lorcaserin in long-term use in obesity studies.[4]
- "Biased" or "functionally selective" 5-HT_{2C} agonism means that it only targets one of the G-protein-coupled receptor (GPCR) pathways, i.e., phospholipase (PLC) without stimulating the other, i.e., β-arrestin (βArr)
- This is of utmost importance because βArr activation is associated with steric hindrance of further 5-HT_{2C} GPCR activation, 5-HT_{2C} receptor internalization and impeding further stimuli of the 5-HT_{2C} receptor[4]

A randomized, double-blind, placebo-controlled Phase 1 study of BMB-101 in healthy volunteers was conducted. The objectives were as follows:

Primary (Safety/Tolerability)

- To investigate the safety and tolerability of BMB-101 following single and multiple oral administration to healthy adults

Secondary (Pharmacokinetics)

- To assess the pharmacokinetic (PK) profiles of BMB-101 following single and multiple oral administration of 4 ascending dose levels in healthy adults
- To investigate the effect of food on the PK of BMB-101 following a single tolerable dose as determined from Part 1 in healthy adults

Exploratory (Target Engagement)

- An exploratory assessment of serum prolactin levels
- An exploratory quantitative electroencephalogram (qEEG) assessment

Study Design

Single Ascending Dose

Single oral dose of BMB-101 or placebo in a fasted state

Cohort 1: 20 mg/70 kg, 6 active, 2 PBO → Cohort 2: 60 mg/70 kg, 6 active, 2 PBO → Cohort 3: 120 mg/70 kg, 6 active, 2 PBO → Cohort 4: 180 mg/70 kg, 6 active, 2 PBO

Food effect

A single dose of BMB-101 120 mg/70 kg was administered in a fed or fasted state

Treatment Period 1 (5 days)		Treatment Period 2 (5 days)
Fed n=6	→	Fasted n=6
Fasted n=6	→	Fed n=6

Without period ≥7 days

Multiple ascending dose

BMB-101 or placebo was administered twice daily (BID) for 7 days, 12 hours apart, with only the morning dose on Day 7

Cohort 1: 40 mg/70 kg, 6 active, 2 PBO → Cohort 2: 80 mg/70 kg, 6 active, 2 PBO → Cohort 3: 120 mg/70 kg, 6 active, 2 PBO → Cohort 4: 150 mg/70 kg, 6 active, 2 PBO

qEEG assessment

Safety and Tolerability

- No serious adverse events were observed, and all adverse events were transient
- The most common adverse effect was oral paresthesia (seen in multiple groups including placebo), related to the sweet taste of the drug product
- The most common on-target adverse events were headache, nausea, and photophobia
  - These are common adverse events for serotonergic drugs
  - Were only observed at the highest dose, which is 2-3 times the predicted therapeutic dose
- Lower incidence of somnolence and GI side effects were observed than with other 5 HT_{2C} agonists

Single Ascending Dose

	Placebo (n=9)	20 mg (n=6)	60 mg (n=6)	120 mg (n=7)	180 mg (n=6)
Oral paresthesia	1 (11.1%)	1 (16.7%)	-	2 (28.6%)	5 (83.3%)
Nausea	-	-	2 (33.3%)	-	3 (50%)
Sedation	-	-	-	-	3 (50%)
Headache	1 (11.1%)	-	-	-	2 (33.3%)
Balance Disorder	-	-	-	-	2 (33.3%)
Photophobia	-	-	-	-	2 (33.3%)
Dizziness	-	-	-	-	1 (16.7%)
Decreased Appetite	-	-	-	1 (14.3%)	-
Euphoria	-	-	-	1 (14.3%)	-

Multiple Ascending Dose

	Placebo (n=8)	40 mg BID (n=6)	80 mg BID (n=6)	120 mg BID (n=6)	150 mg BID (n=6)
Headache	2 (25%)	-	1 (16.7%)	1 (16.7%)	3 (50%)
Balance Disorder	-	-	-	-	3 (50%)
Photophobia	-	-	-	-	3 (50%)
Visual Impairment	-	-	-	1 (16.7%)	-
Oscillopsia	-	-	-	-	1 (16.7%)
Oral Paresthesia	-	1 (16.7%)	1 (16.7%)	1 (16.7%)	-
Nausea	-	-	-	1 (16.7%)	1 (16.7%)
Somnolence	-	-	-	1 (16.7%)	1 (16.7%)
Cognitive Disorder	-	-	-	-	1 (16.7%)
Dizziness	-	-	-	-	1 (16.7%)
Decreased Appetite	-	-	-	-	1 (16.7%)
Dysphoria	-	-	-	1 (16.7%)	-

Pharmacokinetics

- PK dose proportionality in the 40 to 120 mg range was observed in both the SAD and MAD studies
- Food did not affect the AUC, with small Cmax reduction (27%)
- As expected, the PK profile is suitable for BID dosing
- Consistent with Biopharmaceutics Classification System class 1 and high oral bioavailability (>90%), small inter-participant variations were observed (CV<37%)

Dose Proportionality Using a Power Model in the SAD Study (AUC0-t and AUC0-∞)

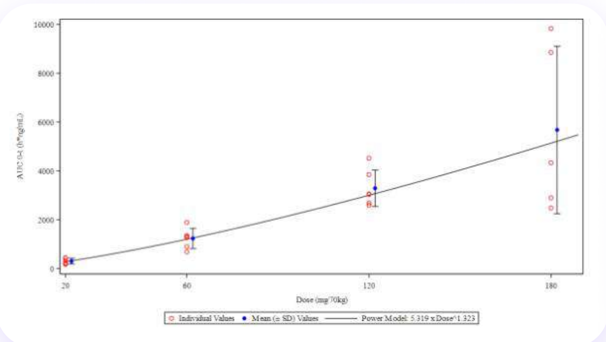


Figure 1.

Mean Concentration in Fed and Fasted Conditions

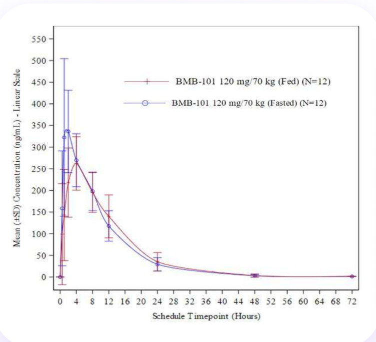


Figure 2.

Steady State (Day 7) PK Profile in the MAD Study

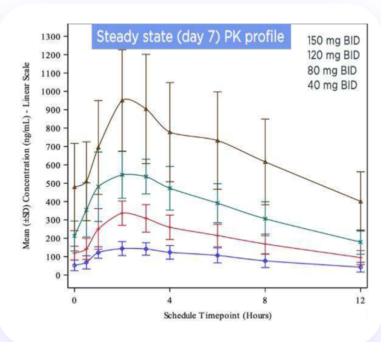


Figure 3.

Target Engagement

Serum prolactin levels

- 5-HT_{2C} agonists (such as lorcaserin and bexicaserin) increase extracellular levels of serotonin which in turn activates the release of prolactin from the anterior pituitary.[5,6]
  - Prolactin is released in a pulsatile fashion when threshold serotonin levels have been reached
  - Typically, a 3-fold increase in prolactin levels is observed when threshold levels of serotonin has been reached
- BMB-101 5-HT_{2C} target engagement was assessed through prolactin levels at 2 hours
- BMB-101 demonstrated transient dose-dependent prolactin release, indicating the receptor activation between 40 and 80 mg BID

Prolactin Levels 2 Hours Post-dose

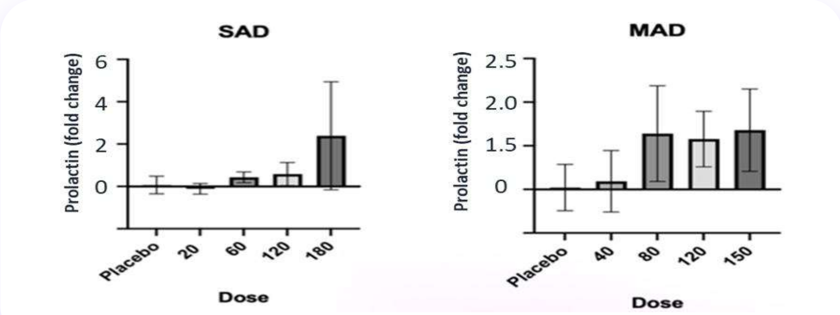
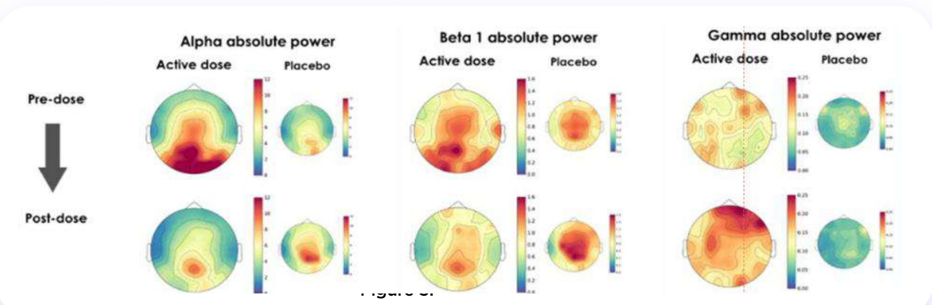


Figure 4.

qEEG

- Central target engagement by qEEG was consistent with other anti-seizure medications
- qEEG demonstrated increased gamma-power, which may indicate additional benefits in cognition

Heat Map of Average EEG Frequency Changes



Changes in absolute power pre/post-dose

	Delta	Alpha	Beta	Gamma
Broad spectrum ASMs				
Valproate	⇩	⇩	⇩	⇩
Leviracetam	⇩	⇩	⇩	NA
Carbamazepine	⇧	⇩	⇩	NA
Lacosamide	⇧	⇩	⇩	NA
5-HT_{2C} agonists				
Bexicaserin	⇧	⇩	⇩	Not reported
BMB-101	⇧	⇩	⇩	⇧

Conclusions

- The Phase 1 trial of BMB-101 demonstrated favorable safety and PK profiles as well as target engagement
- The results support further investigation of BMB-101 in patients with epilepsy
- With its high selectivity and safety, BMB-101 has the potential to be a "best-in-class" 5-HT_{2C} agonist for the treatment of seizures in developmental and epileptic encephalopathy (DEE) and certain forms of generalized epilepsies
- The ongoing Phase 2 BREAKTHROUGH study (NCT06401538) is investigating BMB 101 in the treatment of DEEs and Absence Seizures, conditions characterized by a high proportion of seizures refractory to current treatments

References

1. Higgins et al.Trends Pharmacol Sci. 2013;34(10):560-70
2. Roth. N Engl J Med. 2007;356(1):6-9
3. Rankovic et al. Bioorg Med Chem Lett. 2016;26(2):241-50
4. Felsing et al. Eur J Pharmacol. 2019; 5;848:131-9
5. Gustafson et al. P T. 2013;38(9):525-34.
6. Williams et al. Clin Pharmacol Drug Dev. 2025;doi: 10.1002/cpdd.1602. Epub ahead of print.