Safety, Tolerability, and Pharmacokinetics of Novel 5-HT$_{2C}$ Agonist BMB-101 (Phase I Clinical Study)

#1.532

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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, making its agonists promising candidates for therapeutic interventions. Recently, 5-HT$_{2C}$ agonists demonstrated remarkable efficacy in DEE disorders. Fenfluramine, a non-selective 5-HT agonist with 5-HT$_{2C}$ agonistic properties, is an approved drug for Dravet Syndrome and Lennox–Gastaut syndrome

About BMB-101

A novel scaffold 5-HT2C agonist explicitly designed for chronic treatment of neurological disorders where tolerance and drug resistance are common issues.
Biased agonism / Functional selectivity: BMB-101 works exclusively via the Gq-protein signaling pathway and avoids beta-arrestin activation. This is crucial to minimize the risk of receptor desensitization and tolerance development.
Validated in preclinical models: BMB-101 has demonstrated efficacy in animal models of Dravet Syndrome and several models of generalized seizures (see poster **1.533** for additional details)
A novel mechanism, anti-epileptic drug designed to provide sustained seizure relief in hard-to-treat patient populations

Objectives

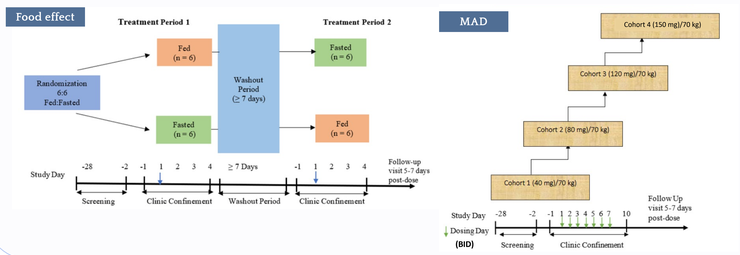
Primary Objective: Safety / Tolerability
· To investigate the safety and tolerability of BMB-101 following single and multiple oral administration to healthy adult subjects.
Secondary Objectives: Pharmacokinetics
· To assess the pharmacokinetic (PK) profiles of BMB-101 following single and multiple oral administration of 4 ascending dose levels in healthy subjects.
· To investigate the effect of food on the PK of BMB-101 following a single tolerable dose as determined from Part 1 in healthy subjects.
Exploratory Objective: Target engagement
· An exploratory assessment of serum prolactin levels
· An exploratory qEEG assessment

Study design

This was a randomized, double-blind, placebo-controlled Phase I study of BMB-101 in healthy human subjects

Single. Ascending Dose: Eligible subjects were assigned to 1 of 4 ascending dose cohorts (20 mg/70 kg to 180 mg/70 kg). Subjects were randomized to receive a single oral dose of BMB-101 or placebo in a fasted state with 6 subjects per cohort receiving BMB-101 and 2 subjects per cohort receiving matching placebo.

Design of Food effects and Multiple Ascending Dose is shown below:



Safety and Tolerability

- No serious adverse effects (SAEs) observed, All AEs were transient
- Most common side effects included oral paraesthesia (possibly related to formulation taste)
- No clinically significant shifts in subject laboratory parameters, vital signs, or EKG parameters during this study

	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%)	-

Single Ascending Dose

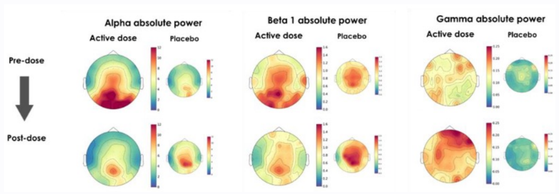
	Placebo (n=8)	40 mg BID (n=6)	80 mg BID (n=6)	120 mg BID (n=6)	150 mg BID (n=6)
Headache	2 (25%)	-	1 (16.7%)	1 (16.7%)	3 (50%)
Balance Disorder	-	-	-	-	3 (50%)
Photophobia	-	-	-	-	3 (50%)
Visual Impairment	-	-	-	1 (16.7%)	-
Oscillopsia	-	-	-	-	1 (16.7%)
Oral Paresthesia	-	1 (16.7%)	1 (16.7%)	1 (16.7%)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

Multiple Ascending Dose

qEEG

- Quantitative electroencephalogram (qEEG) was conducted in the 8 subjects (2 placebo and 6 BMB-101) in Cohort 4 (150 mg/70 kg bid) of the MAD study
- Central target engagement by qEEG in line with other anti-seizure medications
- Potential for improved cognitive performance (increase in gamma power)*

Figure 4 – 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	⇧	⇩	⇩	⇧

Target engagement: prolactin

5-HT$_{2C}$ agonists, such as lorcaserin and bexicaserin, are known to increase prolactin plasma levels via a central mechanism in the hypothalamus. BMB-101 5-HT$_{2C}$ target engagement was assessed through prolactin levels at 2 hours.

Figure 5 – 2h SAD

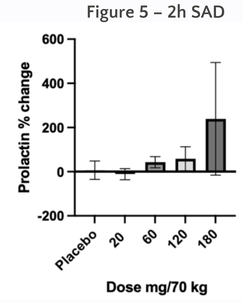
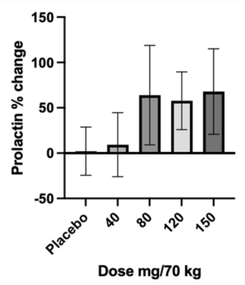


Figure 6– 2h MAD



Pharmacokinetics

- PK dose proportionality in the 40-120 mg range was observed in both SAD and MAD
- Food did not affect AUC with small Cmax reduction 27 %.
- PK profile suitable for BID dosing as expected.
- Consistent with BCS class I and high oral bioavailability (>90%) there are small inter-subject variations observed (CV<37%)

Figure 1 - Dose proportionality using a power model in SAD study: AUC0-t, and AUC0-∞

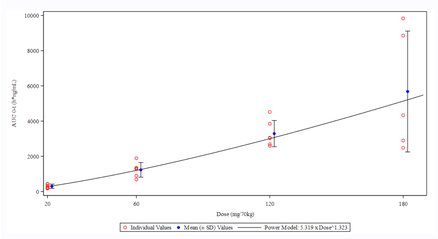


Figure 2 - Mean concentration in fed and fasted conditions

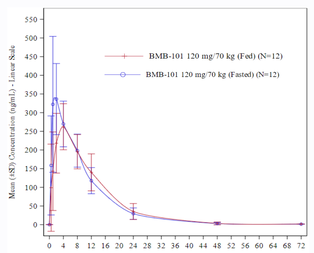
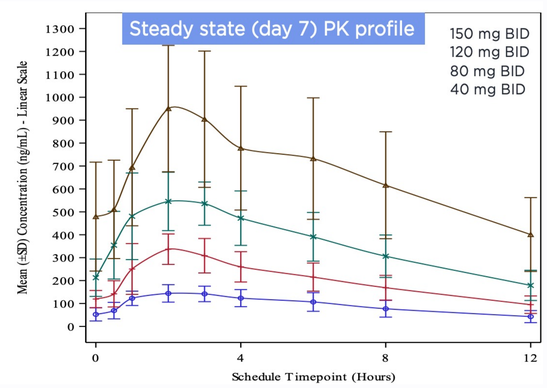


Figure 3– Steady state (day 7) PK profile in MAD study



Conclusions

- The Phase 1 trial of BMB-101 demonstrated a favorable safety and pharmacokinetic profile, as well as target engagement through transient prolactin release and qEEG. These results support BMB-101 further investigation in patients with epilepsy. With its high selectivity and safety, it 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 some forms of generalized epilepsies.
- qEEG demonstrated increased gamma-power, which may indicate additional benefits on cognition
- The phase II BREAKTHROUGH study, is planned for BMB-101 to unravel its potential in treating DEEs and absence epilepsies, conditions characterized by a high proportion of seizures refractory to current treatments.

References:
1. Higgins GA et al. Trends Pharmacol Sci. 2013. 2. Roth BL. N Engl J Med 2007. 3. Rankovic Z, et al. Bioorg Med Chem Lett 2016.
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