BMB-101: A selective 5-HT$_{2C}$ agonist for the treatment of rare epilepsies

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About BMB-101

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 b-arrestin recruitment, which underlines the reduced potential for tolerance.

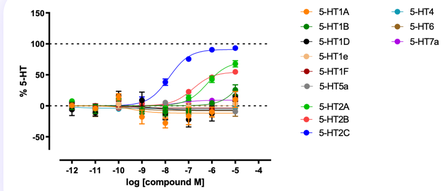
Highly selective 5-HT$_{2C}$ receptor agonist

BMB-101 shows minimal 5-HT$_{2A}$ and 5-HT$_{2B}$ receptor activity and doesn't have liabilities linked with the psychedelic and cardiotoxic effects, respectively[1,2]

Absolute EC$_{50}$ (nM)

Compound	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$
BMB-101	2280	>10000	16.2
Lorcaserin	50.1	67.4	2.4

5-HT$_2$ Gq activation at 50 % serotonin level. Calculated relative to the maximum serotonin activation

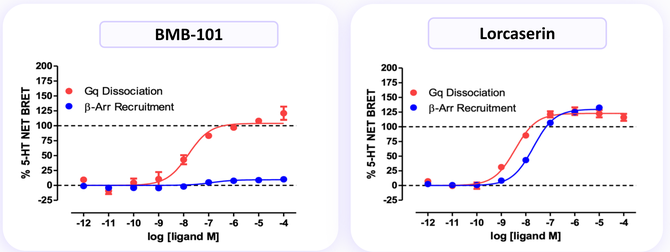


No significant activity at other serotonin receptors

In vitro Pharmacology (John McCorvy group): Effector engagement induced by human 5-HT$_{2C}$ was measured using bioluminescence resonance energy transfer (BRET). Emax was defined relative to serotonin (5-HT).
In addition, the ability of BMB-101 and Lorcaserin to recruit b-arrestin1 and b-arrestin2 was investigated using BRET.

Biased agonism: Lack of beta-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]

About Bright Minds Biosciences

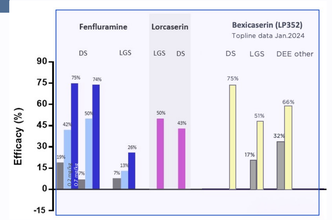
Bright Minds Biosciences is a clinical-stage biotech company developing highly selective 5-HT$_2$ agonists with improved therapeutic profiles for for treatment of neurological and psychiatric disorders

Portfolio of 5-HT$_2$ agonists without 5-HT$_{2B}$ activity

Lead	Features	Development Stage	Indications
5-HT$_{2C}$ agonists for CNS disorders			
BMB-101	• Selective and biased 2C agonist, low 5-HT$_{2A/2B}$ • Biased agonism with minimal b-arrestin recruitment • Suitable for chronic dosing	Clinical Studies – Phase 2 ready	Undisclosed Seizure Disorder Impulsivity Disorders Substance Use Disorder
5-HT$_{2A}$ agonists for the treatment of depression			
BMB-202	• Selective 5-HT$_{2A}$ "Fast-On-Fast-Off" compound • High C_{max} and short plasma half-life • 2-fold more potent than psilocin at 5-HT$_{2A}$	IND-enabling tox	Depression Anxiety PTSD
BMB-xxx	• Mixed 5-HT$_{2A/2C}$ compound • 10-fold more potent than psilocin at 5-HT$_{2A}$	ADMEPK profiling	Neurology / Neuropsychiatric Indication
Low activity 5-HT$_{2A}$ agonists inducing neuroplasticity			
BMB-201	• Non-hallucinogenic 5-HT$_{2A}$ agonists promoting neuroplasticity in brain • Devoid of 5-HT$_{2B}$ activity	IND-enabling studies	Neurology / Neuropsychiatric Indication

Background

The 5-HT$_{2C}$ receptor, a subtype of the serotonin 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.



Note: data from separate clinical trials that had different study designs, for illustrative purposes Lagae, et al (2019).. Frampton, et al (2023). Knupp, et al (2022). Tolete et at (2018). Corporate Presentation Longboard Pharma

Objective

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

Methods

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.

Multiple Ascending Dose

Eligible subjects were assigned to 1 of 4 ascending dose cohorts (40 mg/70 kg to 150 mg/70 kg). Subjects were randomized to receive double-blind treatment of BMB-101 or matching placebo with 6 subjects per cohort receiving BMB-101 and 2 subjects per cohort received matching placebo. Subjects received the study drug twice daily (BID) for 7 days, 12 hours apart (only morning dose on Day 7).

Ph.1 Study Summary

N=76
Drug-placebo ratio 3:1

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

PK
Data not presented
- Dose proportionality observed in SAD and MAD study
- No significant food effects observed

Target engagement
Data not presented
- Transient dose-dependent prolactin release (in SAD and MAD cohorts)
- Effects on qEEG – in line with antiseizure medications

Single Ascending Dose

	Placebo (n=9)	20 mg (n=6)	60 mg (n=6)	120 mg (n=7)	180 mg (n=6)
Oral paresthesias	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 Paresthesias	–	1 (16.7%)	1 (16.7%)	1 (16.7%)	–
Nausea	–	–	–	1 (16.7%)	1 (16.7%)
Somnolescence	–	–	–	1 (16.7%)	1 (16.7%)
Cognitive Disorder	–	–	–	–	1 (16.7%)
Dizziness	–	–	–	–	1 (16.7%)
Decreased Appetite	–	–	–	–	1 (16.7%)
Dysphoria	–	–	–	1 (16.7%)	–

Conclusions

- BMB-101 is potent and selective G-protein biased agonist at 5-HT$_{2C}$ receptor with minimal beta-arrestin recruitment, suggesting lack of tolerance
- The Phase 1 trial of BMB-101 demonstrated a favorable safety and pharmacokinetic profile, supporting its 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.
- Further clinical trials are planned for BMB-101 to unravel its potential in treating DEEs and other rare forms of pediatric epilepsies

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.
4. Felsing DE et al, European Journal of Pharmacology, 2019,