EA DV CONGRESS
AMSTERDAM 25-28 SEPTEMBER 2024
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Abstract N°: 1716

Sphingosine-1-Phosphate Receptor 1 (S1P1) Agonist, Vibozilimod (BS6.890C), Effect on Bradycardia, Preclinical to First-in-human Clinical Translation

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Introduction & Objectives:

Sphingosine-1-Phosphate receptor 1 (S1P1R) modulators have been approved for the treatment of inflammatory and autoimmune disorders. S1P1R stimulation sequesters lymphocyte subsets in peripheral lymphoid organs, preventing inflammation. Due to effects on other subtypes of S1P receptors, these modulators may be associated with first dose effects such as bradycardia and atrioventricular (AV) conduction delays, along with macular edema and bronchoconstriction. Vibozilimod (VBZ, BS6.890C) is a novel S1PR agonist that acts on S1P1R and S1P5R while antagonizing S1P4R with significant lack of activity towards S1P3R. The effects of VBZ on cardiovascular parameters in rats along with results from the first-in-human study are reported here.

Materials & Methods:

VBZ, etrasimod, ozanimod and siponimod were administered intravenously at a dose of 3 mg/kg in anesthetized male Sprague-Dawley rats and their effects on heart rate (HR) and mean arterial blood pressure (MAP) were studied. All agents were infused slowly as solutions in distilled water or PEG-400 after a stabilization period of 20 minutes. In a single ascending dose (SAD) Phase 1 study (n = 6 + 2 placebo), the effects of VBZ on cardiac function in healthy adult males and post-menopausal females were evaluated by measuring heart rate, recording 12-lead ECGs and conducting 24-hour Holter recordings.

Results:

Bradycardia was observed after infusion of all the S1P1R agonists in rats. VBZ infusion was associated with a decrease in heart rate to 130 bpm, which returned to baseline (BL) of 400 bpm within 2 minutes. Etrasimod infusion reduced the HR to 100 bpm and took about 3 minutes to return to the BL of 370 bpm. Ozanimod infusion decreased the HR to 50 bpm, and the effect lasted for 6 minutes before returning to the BL of 360 bpm. However, the reduction in HR with siponimod, which was around 100 bpm, did not return to pre-dose values during the 10-minute recording period (see Fig. 1).

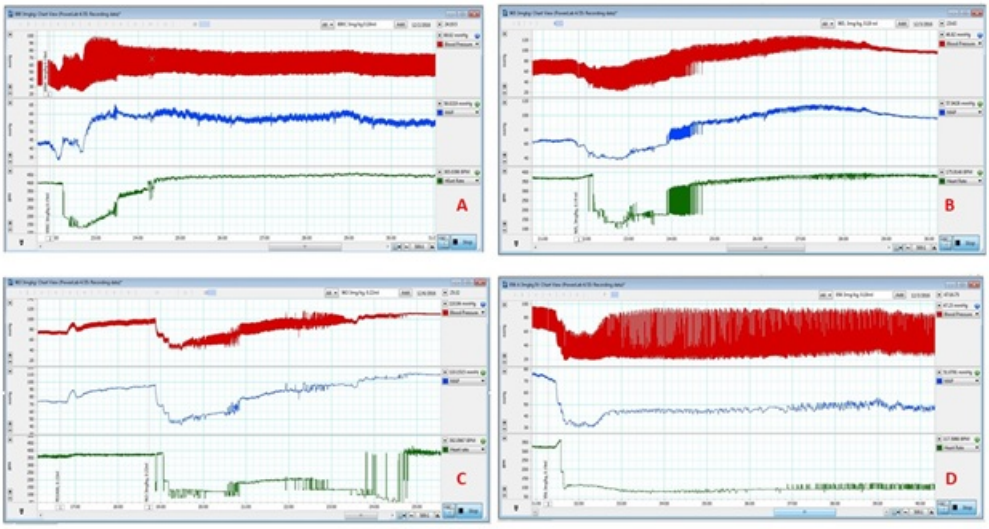
Following administration of VBZ to humans, effects mimicked those observed in the rat model with a dose response observed after doses of 0.1 to 6.0 mg. Mean bradycardia of magnitude greater than 10 bpm was observed following a dose of 1.0 mg or higher. The maximum change in mean (± SD) heart rate from baseline following the administration of single doses of 0.1 mg, 0.3 mg, 1 mg, 2 mg, 4 mg, and 6 mg in males was -2.2 (±3.1), -6.0 (±6), -15.3 (±6), -16.8 (±6.3), -17.2 (±5.9), and -16.5 (±3.9), respectively and for females, it was -15.0 (± 3.5) at 2 mg. The maximum change in HR was transient and observed between 2 to 3 hours following administration of VBZ. None of the treatment groups had a mean HR decrease of more than 10.5 bpm more than

5 hours after administration. Recovery from bradycardia for doses ≥4.0 mg in males and at 2.0 mg in females was faster, after a transient reduction at 2 to 4 hours, suggesting that subjects adapt and develop more rapid tolerance with higher exposure to VBZ. The mean change in HR from baseline is presented in Table 1. Thus, the observed bradycardia in humans closely resembled observed in the rat model.

Conclusion:

VBZ, a differentiated agonist at S1P1 and S1P5 receptors produced only a transient and well manageable effect on heart rate in humans, with faster recovery as observed in the preclinical model. Thus, the effects of VBZ observed in animal studies were successfully translated in humans in terms of reduction in magnitude of heart rate in Phase I study, thus providing improved safety on cardiac function.

Figure 1: Effects of different compounds on heart rate, blood pressure, and mean arterial pressure in anesthetized Sprague-Dawley rats



Changes in blood pressure (BP-Red line in mm of Hg), mean arterial BP (MAP-Blue line in mm of Hg) and heart rate (HR-green line in beats per minutes, bpm) were monitored continuously using a PowerLab® data acquisition system with LabChart 8 software (AD Instruments). X-axis represents time in minutes.

HR decrease (Bradycardia) : Vibozilimod (A)< Etrasimod (B)< Ozanimod (C)<Siponimod (D)
MABP change : Vibozilimod (A)<Siponimod (D)<Ozanimod (C)<Etrasimod (B)
The observed changes with Vibozilimod (VBZ) being transient and minimal in all the parameters

Table 1: Summary of Mean Change in Heart Rate (bpm) from Baseline (Δ) by dose level in Phase 1 Single Ascending Dose Study of Vibozilimod

Time (h)	0.1 mg	0.3 mg	1 mg	2 mg (M)	2mg (F)	4 mg	6 mg	Placebo
N	6	6	6	6	6	6	6	14
BL	56.8 ± 7.4	55.0 ± 6.1	60.8 ± 11.7	61.5 ± 7.5	61.2 ± 6.3	59.5 ± 5.6	56.2 ± 2.1	60.0 ± 10.8
0.5	0.8 (3.1)	1.2 (2.0)	0.8 (3.2)	0.2 (4.0)	-0.3 (5.2)	0.3 (2.1)	1.8 (4.5)	-0.9 (3.5)
1	1.7 (2.6)	0.7 (2.8)	-4.7 (4.4)	-6.3 (6.5)	-9.7 (4.3)	-8.3 (8.2)	-8.3 (4.9)	-1.1 (3.4)
2	-2.2 (3.1)	-4.7 (4.7)	-13.2*** (4.4)	-16.8*** (6.3)	-15.0*** (3.5)	-17.2*** (5.9)	-16.5*** (3.9)	0.2 (5.1)
3	-1.3 (4.1)	-6.0 (5.3)	-15.3*** (6.0)	-16.3*** (7.1)	-13.7*** (5.1)	-15.0*** (5.4)	-15.5*** (3.8)	-0.4 (4.0)
4	-0.8 (3.1)	-6.0 (6.0)	-14.3*** (6.2)	-13.8*** (7.4)	-11.0* (4.6)	-13.2*** (8.6)	-14.3*** (3.1)	0.6 (4.7)
5	5.7 (3.2)	5.0 (5.3)	-4.2 (5.3)	-6.5 (6.1)	-4.7 (4.5)	1.8 (8.6)	-1.5 (5.0)	15.9*** (9.3)
24	0.0 (3.2)	0.8 (4.5)	-5.3 (3.7)	-7.8 (6.7)	-3.8 (4.5)	-1.5 (4.8)	-6.3 (5.5)	1.4 (4.1)

Values are expressed as mean (±SD); BL – Baseline
For statistical analysis heart rate, entire data from pre-dose to EOS (Day 14) h was used; only data at BL, 0.5h, 1h, 2h, 3h, 4h, 5h, and 24 h represented in the table.
*p<0.05, **p<0.01, ***p<0.001 vs respective group BL heart rate. Two-way ANOVA followed by Bonferroni's test