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Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vibozilimod: A Randomized, Double-blind, First-in-human, Study in Healthy Male and Female Subjects

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Introduction & Objectives:

Vibozilimod (VBZ) is a potent, oral, selective agonist of the sphingosine-1-phosphate receptors (S1PR) 1 and 5, an inverse agonist at S1P4R, and devoid of activity on S1P3R. S1P1 receptor modulators sequester circulating lymphocytes within lymph nodes, causing reduction of pathogenic autoimmune cells in the blood stream and inflamed tissues, making S1P1R agonists an effective therapeutic agent for autoimmune disorders. VBZ is in clinical development for the treatment of chronic immune-mediated, inflammatory disorders.

Materials & Methods:

In this randomized, double-blind, phase 1, single ascending dose study, healthy male and post-menopausal female volunteers received single doses of either VBZ 0.1, 0.3, 1, 2, 4, or 6 mg in males and 2 mg in post-menopausal females, or placebo in a 3:1 ratio. Safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) were evaluated.

Results:

Fifty-six healthy subjects were randomly assigned to VBZ or placebo in seven groups (groups 1 to 6; males: n=48, and group 7; females: n=8). Vibozilimod was well tolerated and adverse events (AE) were mild to moderate. Transient bradycardia was noted between 2 and 4 h post-dose, the maximum drop in heart rate was 17.2 beats/min, which plateaued at 2 mg and higher doses (Table 1). A dose-dependent percent reduction of absolute lymphocyte count (ALC) compared to baseline was observed, with onset at approximately 4 h post-dose, 30.9 ($p<0.05$), 50.0 ($p<0.001$), 43.6 ($p<0.01$), 58.6 ($p<0.001$), 60.5 ($p<0.001$) and 68.1 ($p<0.001$), vs. placebo (PBO) 22.4 and at 24 h with 21.0 (non-significant; ns), 32.1 ($p<0.05$), 36.3 (ns), 51.8 ($p<0.001$), 57.0 ($p<0.001$) and 74.0 ($p<0.001$), vs. PBO 17.7 at doses of 0.3, 1.0 , 2.0, 2.0 (F), 4.0 and 6.0 mg respectively. Nadir ALC observed between 4-12 h and was similar to 4 h effect, whereas at highest dose of 6 mg the percent reduction was 77.0 (<0.001). However, at 96 h the ALC changes were non-significant other than at the 6 mg dose. The ALC effects were rapid and resolved within 96h (Table 2).

Vibozilimod showed dose proportional pharmacokinetic parameters of maximum concentration (Cmax) and area under the curve (AUC). The mean time to maximum concentration (tmax) was between 2 h and 2.5 h, and the median t1/2 was between 33 h and 37 h. Exposure was higher in females than in male subjects. The Vd/F was in the range of 232 L to 299 L in males and 165 L in females, however with comparable t1/2 in both (Table 2).

Conclusion:

Vibozilimod was well-tolerated with only mild to moderate adverse events (AEs) up to a dose of 6 mg. Transient bradycardia, a known class effect, was observed with a mean heart rate reduction of less than 10 beats/min up to a dose of 0.3 mg. Bradycardia effects plateaued at doses of 2 mg and above. Dose dependent reductions in ALC were significant at doses of 0.3 mg and above. Demonstrated a dose proportional and favorable PK profile. Vibozilimod is a potent sphingosine agonist with potential promise for the treatment of immune disorders such as inflammatory bowel disease, multiple sclerosis, lupus, psoriasis, atopic dermatitis, and alopecia areata.

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
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)

Values are expressed as mean (±SD); BL – Baseline; bpm-beats per minute; F-Female
For statistical analysis of heart rate, entire data from pre-dose to EOS (Day 14) h was used; only data at BL, 1h, 2h, 3h, 4h, and 5h, 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

Table 2: Summary of Mean Change in Absolute Lymphocyte Count (ALC) from Baseline (Δ) and PK parameters by dose level in phase 1 Single Ascending Dose Study of Vibozilimod

Dose	Sex	ALC (Lymphocytes/µL blood) [Mean ± SD]					Mean PK Parameters			
(N)		BL	4h	Nadir	24h	96 h	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	Vd /F (L)
Placebo (14)	Male, Female	2226.4 ± 379.1	1727.1 ± 423.7 (-22.4)	1727.1 ± 423.7 (-22.4)	1839.3 ± 451.8 (-17.7)	1958.6 ± 386.6 (-11.6)	----	----	----	----
0.1 mg (6)	Male	2078.3 ± 596.6	1666.7 ± 337.9 (-17.8)	1666.7 ± 337.9 (-17.8)	1873.3 ± 433.8 (-7.4)	1933.3 ± 337.4 (-1.5)	0.67	17.83	35.47	200.28
0.3 mg (6)	Male	2851.7 ± 525.2	1986.7 ± 589.5* (-30.9)	1971.7 ± 565.2* (-31.1)	2268.3 ± 507.7 (-21.0)	2383.3 ± 460.4 (-16.3)	1.85	55.76	34.45	235.86
1 mg (6)	Male	2576.7 ± 557.9	1291.7 ± 300.7*** (-50.0)	1160.0 ± 278.6*** (-55.0)	1721.7 ± 255.3* (-32.1)	1968.3 ± 457.1 (-23.6)	6.03	185.83	32.67	249.55
2 mg (6)	Male	2078.3 ± 355.4	1130.0 ± 315.4** (-43.6)	1020.0 ± 394.3*** (-49.0)	1281.7 ± 432.5 (-36.3)	1671.7 ± 485.4 (-20.1)	9.74	324.71	34.31	305.09
2 mg (6)	Female	2441.7 ± 464.2	981.7 ± 107.2*** (-58.6)	851.7 ± 178.8*** (-64.5)	1181.7 ± 399.0*** (-51.8)	1716.7 ± 213.8 (-28.8)	19.94	551.47	32.54	166.77
4 mg (6)	Male	1908.3 ± 477.9	743.3 ± 265.7*** (-60.5)	713.3 ± 102.5*** (-60.4)	775.0 ± 103.3*** (-57.0)	1375.0 ± 343.1 (-26.3)	22.61	720.03	37.18	284.76
6 mg (6)	Male	1995.0 ± 306.9	636.7 ± 208.9*** (-68.1)	440.0 ± 122.1*** (-77.0)	505.0 ± 115.4*** (-74.0)	1156.7 ± 108.4* (-40.6)	33.66	1207.29	36.2	295.68

AUC- Area under the curve; BL – Baseline; C_{max} – maximum concentration; PK – Pharmacokinetic; $t_{1/2}$- terminal half-life; V_d/F- apparent volume of distribution. Values in parasthesiae indicate percent changes from BL.
For PK parameters, C_{max} and AUC are geometric means, $t_{1/2}$ is median; Vd/F is arithmetic mean.
For statistical analysis of absolute lymphocyte count, entire data from pre-dose to EOS (Day 14) h was used; only data at BL, 4h, 24 h and 96 h represented in the table.
*P<0.05, **P<0.01, ***P<0.001 vs. respective group BL values, Two-Way ANOVA followed by Bonferroni's test.