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Pharmacokinetics and pharmacodynamics of OPL-002, a highly selective S1P1R modulator, in healthy adult volunteers

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Abstract

BACKGROND: Sphingosine 1-phosphate-1 receptor (S1P1R) modulators are effective for ulcerative colitis (UC), but current compounds have limitations, including liver function test (LFT) elevations and first dose heart rate (HR) reduction. OPL-002 is a selective and orally bioavailable small molecule S1P1R modulator in development for UC designed to mitigate these limitations.

OBJECTIVE: To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of OPL-002 in a Phase 1 study in normal healthy volunteers.

METHODS: During the single ascending dose (SAD) period, OPL-002 or matching placebo was administered orally as a single dose in 6 cohorts (2.5, 4, 10, 15, 25, and 40 mg). During the multiple ascending dose (MAD) period, OPL-002 or matching placebo was administered daily for 21-28 days in 5 cohorts (2 mg cohort 21 days without titration, 10 and 20 mg 14 days of target dose after 7 days of titration, and 35 and 45 mg 21 days after 7 days of titration). Each of the SAD and MAD cohort was randomized to OPL-002 (n=6) or placebo (n=2). Food effect was assessed in the 15 mg cohort after a 7-day wash out period.

Absolute lymphocyte reduction was captured as a pharmacodynamic (PD) biomarker throughout the study. Heart rate (HR) was monitored via Holter from -1 to 24 hours during SAD and with each dose change during MAD. During SAD, plasma for PK was collected for 72 hours after study drug administration. During MAD, plasma for PK was collected throughout the study and for 72 hours after the last dose.

RESULTS:

PK: Single dose of OPL-002 was characterized by a Tmax of 1.5 to 2.0 hours postdose and terminal half-life of approximately 19 to 23 hours (Figure 1). There was no food effect. Following multiple doses of OPL-002, exposure was dose-proportionate with steady-state reached after 4 to 7 days of target-dose exposure.

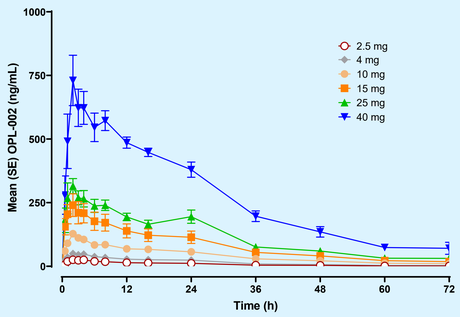
PD: In SAD, OPL-002 led to dose-dependent reductions in absolute lymphocyte counts with maximum reduction occurring at 2 to 3 hours after dosing (Figure 2, left). A single dose of 40 mg was associated with a reduction of ~65% in total peripheral blood lymphocyte counts. Lymphocyte counts rapidly returned to near-Baseline 72-hours after dose. In MAD, daily dosing of OPL-002 led to a dose-dependent steady state reduction in absolute lymphocyte count (Figure 2, right). At the higher doses of 35 mg and 45 mg, the steady state mean reduction in lymphocyte counts were 62% and 65%, respectively. Lymphocyte counts returned to normal or were rapidly returning to normal by 72 hours after the last dose of drug.

Safety: There were no serious adverse events. None of the subjects had LFT elevations, pulmonary function or ocular abnormalities, or other notable safety findings. During MAD, the only adverse events (AEs) reported in >1 subject in any of the OPL-002 treatment groups were contact dermatitis (associated with prolonged ECG electrode placement associated with Holter monitoring), and oropharyngeal pain, reported in 2 (33%) subjects in the 20 mg group and 1 (10%) in the placebo group. Treatment initiation was associated with transient dose-dependent decreases in HR at >4 mg in the SAD study (Figure 3, left). With doses up to 45 mg (preceded by 7-days of dose titration), the maximum decrease from baseline in HR in the MAD study was 3.5 beats-per-minute with nadir at 1 hour in the 35 mg group (Figure 3, right). The first full dose of 20 mg was administered after a drug holiday, and therefore those data are not included. There were three transient and asymptomatic events of AV block with one event of 1st degree block in 35 mg MAD on Day 8 and two events of 2nd degree Type 1 AV block (1 at 10 mg titration dose in the 20 mg MAD group and 1 at 40 mg in the SAD group).

Results

Figure 1: PK Results

SAD



MAD

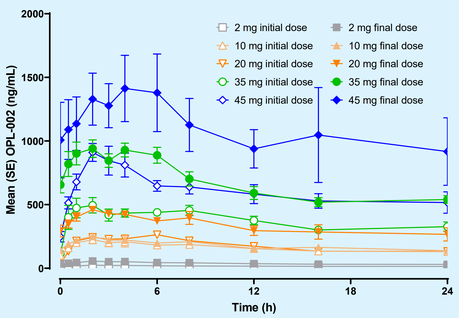
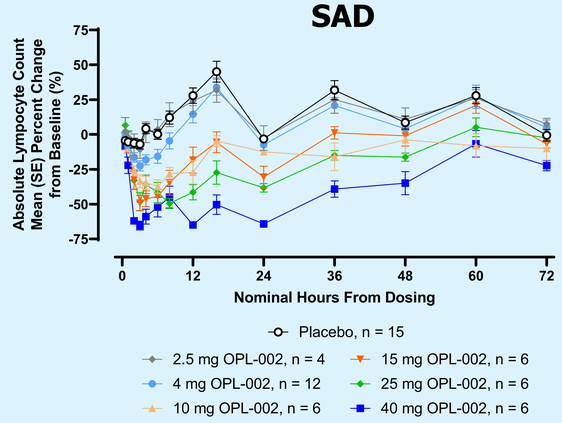


Figure 2: PD Results

SAD



MAD

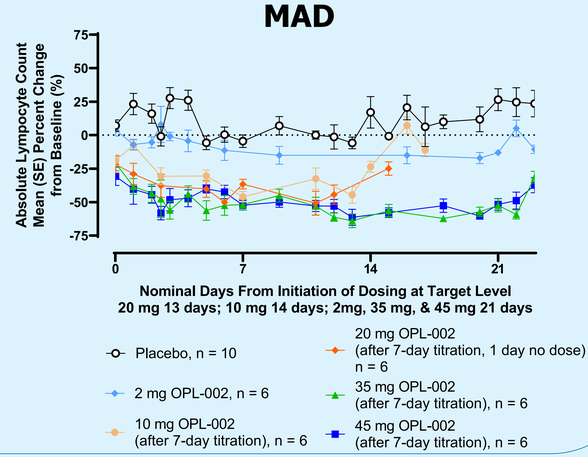
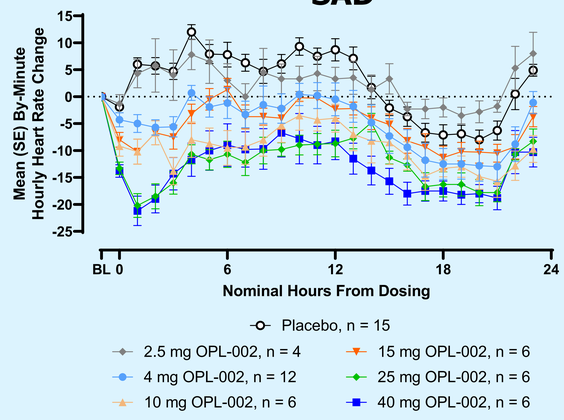
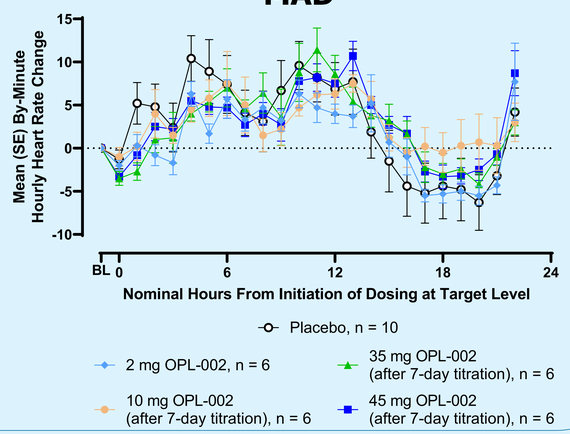


Figure 3: Heart Rate

SAD



MAD



Conclusions:

- **OPL-002 was well tolerated in healthy adults at all single and multiple doses of up to 45 mg. There was no signal for LFT changes, pulmonary function or ocular exam abnormalities**
- **OPL-002 exhibited potent and rapid dose dependent lymphocyte reduction with rapid lymphocyte recovery**
- **There was no clinically significant first dose HR reduction during treatment for up to 21 or 28 days**