A Phase I Study Allowing Clinical Screening of Multiple Solubility-Enhancement Formulation Technologies, and an Assessment of Food, PPI and Dose Linearity Assessment with the Selected Formulation of BOS172767, in Healthy Volunteers

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PURPOSE

BOS172767 is a first in class small molecule inverse agonist of retinoic acid-related orphan nuclear receptor gamma-t, being developed for the treatment of autoimmune diseases. Safety and tolerability have been demonstrated in a previous first in human (FIH) Phase 1 study using a simple API blend in capsule. Low oral exposure, non-linear pharmacokinetics (PK), high variability and a large positive food effect were observed. Therefore, a solubility-enhanced formulation was considered necessary to help overcome these PK challenges and identify a formulation suitable for long-term clinical development.

Formulations were developed and screened using an integrated platform of real-time adaptive GMP manufacturing and clinical testing. The study was designed to assess the clinical performance of three prototype formulations, assess food effect and dose linearity of a selected formulation and also the impact on exposure in subjects taking proton pump inhibitors (PPI). The clinical PK data generated in the study would then be utilized to select a formulation for further development.

METHOD(S)

Three different formulations, representing different strategies (micronized capsule, lipid capsule, and spray dried dispersion [SDD] tablet) were developed and assessed in a pH shift biorelevant dissolution test using fasted state simulated gastric and simulated intestinal fluid. The aim of the biorelevant dissolution test was not to rank order the formulation platforms but rather identify optimal dissolution profiles for each platform. An integrated Translational Pharmaceutics program was designed to evaluate the human PK of the multiple formulations manufactured to GMP at small-scale. An adaptive design allowed a within-trial decision (see schematic) to select the optimal formulation for additional clinical testing in the same study protocol.

The study was open label, with two parts in healthy subjects. Part 1 was a 6-period sequential, partially randomized study, in which 12 subjects received three formulation prototypes and the IR reference capsule at 200 mg in the first four periods. After period 4 the lead formulation prototype was then selected for dosing in the fasted and fed state. The lead formulation advanced to optional Part 2, a 4-period sequential study in 10 healthy subjects, assessing exposure at 3 single ascending dose levels and in subjects taking PPI.

RESULT(S)

In vitro dissolution testing demonstrated that all three formulation technologies had greater % release (50 to 63 %) compared to the FIH API blend in capsule and IR reference capsule, which had < 20 and < 10 % at 90 minutes, respectively.

In Part 1, all prototype formulations at 200 mg (SDD tablets, lipid capsules and micronized capsules) showed an increase in exposure (Cmax and AUC(0-last)) over the IR reference capsule (Figure 1), with all prototype formulations showing similar AUC(0-last). The SDD tablet had the highest exposure showing an approximate 10-fold increase in Cmax and a 2-fold increase in AUC(0-last) compared to the reference capsule. The micronized capsule was selected for progression due to future manufacturing considerations, similar exposure to that of the SDD tablet, and a lower observed Cmax which could potentially provide an improved safety profile.

The micronized capsule was then dosed at 100 mg in the fed (high fat meal) and fasted state during periods 5 and 6. Cmax increased by > 2-fold, however the AUC(0-last) was similar to that in the fasted state. The magnitude of the food effect was reduced compared to that observed in the previous study with the FIH API blend in capsule, whereby a 5.6 and 3.2-fold increase in Cmax and AUC(0-6) was observed with a 200 mg dose, respectively. A level C in vitro in vivo correlation (IVIVC) was achieved for % dissolution at 90 minutes and AUC(0-last) (Figure 2), thus the biorelevant dissolution test has been shown to be clinically relevant.³

In Part 2, with dose escalation of the micronized capsule at 400 mg, 600 mg and 800 mg exposure increased in an approximate dose proportional manner, although data was highly variable (Table 1). Previously, with the API blend in capsule systemic exposure had plateaued at 200 mg. Co-administration with the PPI rabeprazole resulted in minimal effect on exposure (Table 1). Overall the incidence of adverse events for Part 1 and 2 was low, with no SAEs.

CONCLUSION(S)

Translational Pharmaceutics was used to evaluate three BOS172767 formulations in one integrated clinical study, and successfully identified the micronized capsule as the new lead formulation. This formulation had superior exposure compared to the IR reference capsules, and approximate proportional increase in exposure up to 600 mg. The food effect observed at 100 mg was reduced compared to that previously seen at 200 mg (FIH capsule) and elevated gastric pH (subjects taking PPIs) had minimal effect on exposure. A Level C IVIVC was achieved with a biorelevant dissolution test, which provides valuable information for future formulation development and setting of product specifications.

REFERENCES


Table 1. Summary of the Geometric mean (%CV) Key Pharmacokinetic Parameters of BOS1727670 in healthy volunteers following oral administration of Micronized Capsule - Part 2

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Tmax (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC (0-48h) (h*ng/mL)</th>
<th>AUC (0-inf) (h*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (N=10)</td>
<td>3 (1, 2.4)</td>
<td>41.5 (66.7)</td>
<td>828 (67.1)</td>
<td>(n=2)</td>
</tr>
<tr>
<td>600 mg (N=10)</td>
<td>2.51 (1.36)</td>
<td>55.5 (93.5)</td>
<td>1320 (80.2)</td>
<td>-</td>
</tr>
<tr>
<td>800 mg (N=8)</td>
<td>3 (1, 6)</td>
<td>78.9 (121)</td>
<td>1600 (82.6)</td>
<td>2850 (88.2) (N=6)</td>
</tr>
<tr>
<td>800 mg + PPI (N=6)</td>
<td>4.51 (2, 24)</td>
<td>47.4 (68.8)</td>
<td>1160 (73.2)</td>
<td>2350 (38.4) (N=6)</td>
</tr>
</tbody>
</table>

*Median (range), mg = milligram, H = hour, ng = nanogram, mL = millilitre, N = number, CV = coefficient of variation

Figure 1: Mean Plasma BOS172767 Concentration-Time Profiles after Oral Dosing on Semi-Log Scale (Part 1)

Figure 2: Level C IVIVC – Correlation between % dissolution at 90 minutes and AUC(0-last) for solubility-enhanced formulation prototypes and API reference capsules