INTRODUCTION

• Second-generation Bruton’s tyrosine kinase (BTK) inhibitor, a nonselective enzyme belonging to the TEC kinase family, is critical to B-cell proliferation, survival, trafficking, and downstream signaling of the B-cell receptor in regulating multiple cellular processes

• BTK Inhibitor Resistance: The irreversible BTK inhibitor ibrutinib and acalabrutinib have demonstrated effectiveness in various B-cell malignancies1-4; however, resistance occurred to ibrutinib, due to the Cyso481Ser mutation on the kinase active site, has been reported, resulting in substantially reduced activity.1,5 Development of Cyso481 resistance mutations has been anticipated in response to acalabrutinib exposure, as reported for a patient with malignancies in a phase 1 clinical trial.

• Activity: SNS-062 is a reversible noncovalent inhibitor of BTK, in development for the treatment of B-cell malignancies and other cancers.

This compound was shown to inhibit BTK activity at 0.1 nM Compound (IC50) concentration of 0.4 nM, 24 nM, and 19 nM, respectively, in vitro kinase assays, SNS-062 inhibited BTK, ITK, and TEC with IC50 values of 0.4 nM, 24 nM, and 19 nM, respectively, and demonstrated no significant inhibition against ITK and TEC (2,000 nM). The kinase selectivity profile of SNS-062 may result in improved safety and tolerability over existing BTK inhibitors due to these differences in selectivity.

OBJECTIVES

• This study evaluated safety, pharmacokinetics (PK), and pharmacodynamics (PD) after a single dose of SNS-062 administered to healthy subjects

METHODS

• This is a first-in-Human Phase 1A randomized, double-blind, placebo-controlled, single-dose study, conducted in 3 stages. 1

• In Stage 1, sequential cohorts of 8 subjects each were randomly assigned to receive progressively higher single oral administrations of SNS-062 at doses of 10, 30, 100, and 300 mg [n=6 per cohort; 3 males and 3 females] or placebo. All subjects received 100% active drug in the placebo arm.

• Stages 2 and 3 will evaluate the effects of food and CYP3A4 inhibitors on SNS-062 exposure, respectively, on the PK of SNS-062 and are ongoing

• The primary endpoint of safety was assessed by monitoring adverse events, vital signs, clinical laboratory tests, 12-lead ECG, and changes in cardiac biomarkers

RESULTS

Patient Demographics

• The median age for the 24 subjects who received SNS-062 was 55 years (range: 22-64), among the 8 subjects who received placebo, the median age was 42.5 years (range: 29-65). A majority of the subjects who received SNS-062 were Caucasian (95.8%); only 1 subject in cohort 1 (4.2%) was an Asian

SAFETY FINDINGS

• Treatment-emergent AEs (TEAEs) were reported for 8 (33%) subjects who received SNS-062 and for 3 (38%) subjects who received placebo (Table 2). 6 (25%) subjects who received SNS-062 had treatment-related TEAEs compared with 3 (38%) subjects who received placebo.

• For subjects who received SNS-062, treatment-related TEAEs included headache, nausea, and supraventricular tachycardia; additional reported TEAEs included conjunctivitis, rhinorrhea, and otitis media. No obvious pattern of dose-dependent toxicity was observed.

• In the placebo group, all TEAEs were considered treatment-related and included headache, nausea, and dizziness.

• AEs were all reported as Grade 1 except for 1 subject (who received 300 mg SNS-062 who experienced Grade 2 headache and fatigue).

• No Grade 3 or higher AEs were reported

• There were no serious adverse events reported.

• The extent of pBTK inhibition at different plasma concentrations is shown in Figure 5 for a specific target level of pBTK inhibition for clinical efficacy has not yet been reported, it is expected that the IC50 pBTK inhibition is generally sufficient for clinical activity4,8.

CONCLUSIONS

• SNS-062 showed favorable safety and PK/PD profiles in healthy subjects

• SNS-062 exposure at the lowest dose of 50 mg exceeded exposures reported for both ibrutinib and acalabrutinib when administered at their respective recommended dose levels. (Table 3)

• The extent of pBTK inhibition at different plasma concentrations is shown in Figure 5. It is clear that a specific target level of pBTK inhibition for clinical efficacy has not yet been reported, it is expected that the IC50 pBTK inhibition is generally sufficient for clinical activity.

Figure 5. Percent BTK Inhibition vs SNS-062 Plasma Concentration

Table 2. Summary of SNS-062 Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Cohort 3 (300 mg)</th>
<th>Cohort 2 (200 mg)</th>
<th>Cohort 1 (150 mg)</th>
<th>Placebo</th>
<th>DL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-24h) (ng•hr/mL)</td>
<td>19,136 (17,645)</td>
<td>13,712 (11,468)</td>
<td>11,850 (10,462)</td>
<td>3,209 (2,873)</td>
<td>5,807 (4,977)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7,302 (6,344)</td>
<td>4,612 (3,819)</td>
<td>3,763 (3,192)</td>
<td>0.668 (0.393)</td>
<td>2.15 (1.62)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>6.9 (6.6)</td>
<td>7.3 (6.3)</td>
<td>5.8 (5.1)</td>
<td>3.2 (2.5)</td>
<td>3.1 (3.1)</td>
</tr>
</tbody>
</table>

AUC and Cmax were calculated using the noncompartmental method from 0 to 24 hours for both oral and intravenous dosing. AUC represents the area under the plasma concentration-time curve (AUC), maximum plasma concentration (Cmax), and time of maximum concentration (Tmax), expressed as mean (SD).

PRODUCT INFORMATION

IMBRUVICA® (ibrutinib) capsules, for oral use [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC.; 2016.


In patients with advanced B-cell malignancies with and without the Cys481 resistance mutation, SNS-062 demonstrated rapid, profound (~100%), and prolonged inhibition of pBTK at all dose levels, as shown in Figure 4.