Safety and Pharmacokinetics of the Oral Iron Chelator SP-420 in β-thalassemia

Ali T Taher1, Antoine N Saliba2, Kevin H Kuo3, Patricia J Giardina4, Alan R Cohen5, Ellis J Neufeld6, Yesim Aydinok7, Janet L Kwiatkowski5, Brenda I Jeglinski8, Keith Pietropaolo8, Gregory Berk8, Vip Viprakasit9

1Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; 2Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; 3Division of Medical Oncology and Hematology, University Health Network, Toronto, ON, Canada; 4Weill Medical College of Cornell University, New York, NY, USA; 5Division of Hematology, The Children's Hospital of Philadelphia and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; 6St. Jude Children's Research Hospital, Memphis, TN, USA; 7Department of Pediatric Hematology, Ege University Hospital, Izmir, Turkey; 8Sideris Pharmaceuticals, Inc., Lexington, MA, USA; 9Department of Pediatrics & Thalassemia Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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* Corresponding authors:
Ali T. Taher, MD, PhD, FRCP, Department of Internal Medicine, American University of Beirut Medical Center, Cairo Street, PO Box 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon; Fax: (011) 961-1-370814; ataher@aub.edu.lb

Vip Viprakasit, MD, DPhil (Oxon), Siriraj Integrated Center of Excellence for Thalassemia (SiiCOET), Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand; Tel/Fax: +66-2-4122113, vip.vip@mahidol.ac.th

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Abstract

Our Phase I, open-label, multi-center, dose-escalation study evaluated the pharmacokinetics (PK) of SP-420, a tridentate oral iron chelating agent of the desferrithiocin class, in patients with transfusion dependent β-thalassemia. SP-420 was administered as a single dose of 1.5 (n=3), 3 (n=3), 6 (n=3), 12 (n=3), and 24 (n=6) mg/kg or as a twice-daily dose of 9 mg/kg (n=6) over 14-28 days. There was a near dose-linear increase in the mean plasma SP-420 concentrations and in the mean values for $C_{\text{max}}$ and $AUC_{0-\tau}$ over the dose range evaluated. The median $t_{\text{max}}$ ranged from 0.5 – 2.25 h and was not dose-dependent. The study was prematurely terminated by the sponsor due to renal adverse events including proteinuria, increase in serum creatinine, and one case of Fanconi syndrome. Other adverse effects included hypersensitivity reactions and gastrointestinal disturbances. Based on current dose administration, the renal adverse events observed outweighed the possible benefits from chelation therapy. However, additional studies assessing efficacy and safety of lower doses or less frequent dosing of SP-420 over longer durations with close monitoring would be necessary to better explain the findings of our study and characterize the safety of the study drug.
Introduction

Transfusion-dependent thalassemia (TDT) encompasses a group of thalassemic patients who are chronically dependent on regular transfusions. With repeated transfusions, patients with TDT accumulate iron in various organs including the heart, liver, and endocrine glands. Iron chelators are small molecules that form complexes with iron and promote iron excretion in patients with iron overload. Three iron chelating agents – deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) – have been approved by the Food and Drugs Administration and European Medicines Agency for the treatment of transfusional iron overload in patients with TDT. Each of the approved iron chelating agents has been proven to be effective in iron removal with different safety profiles. Consistent use of iron chelation therapy remains of fundamental importance to control systemic iron burden and complications associated with iron overload as a lifelong treatment. However, each of the approved iron chelating agents has challenging properties such as burdensome administration, suboptimal tolerability or unfavorable clinical and laboratory adverse effect profiles. Parenteral administration of DFO over 8 hours for five to seven nights per week can be troublesome, time consuming, and painful. DFO also requires monitoring for ocular toxicity, ototoxicity, and growth retardation. DFP is an oral iron chelating agent but requires frequent dosing – three times daily – which may also have a negative impact on compliance. In addition to gastrointestinal disturbances and arthropathy, drug-related adverse effects of DFP also include the rare, but potentially dangerous, neutropenia and agranulocytosis necessitating frequent blood count monitoring. DFX, another oral iron chelating agent, is also associated with gastrointestinal disturbances that may affect compliance with therapy. Moreover, DFX therapy is associated with renal toxicity and hepatotoxicity. DFX is contraindicated in patients with estimated creatinine clearance <40 mL/min or serum creatinine >2 times the upper limit of normal. Gastrointestinal hemorrhage is another rare but potentially serious complication associated with DFX therapy. As a result, no currently approved chelator can be regarded as ideal; hence, the search for the ideal iron chelator with proven safety, tolerability, and efficacy continues.

SP-420 is a tridentate iron chelator of the desferriothiocin class that chelates iron with a stoichiometry of 2:1 SP-420:Fe(III). SP-420 is an analog of deferitrin, an experimental compound that showed clinical efficacy but was discontinued from further development due to renal toxicity in patients. Structure-activity studies with analogs of deferitrin demonstrated that kidney toxicity could be minimized by the addition of polyethers to the phenol ring.
The location and length of the polyether substituent were optimized in the rat model to improve pharmacokinetics (PK), tissue distribution and iron chelating efficiency, and to reduce kidney toxicity, leading to the discovery of SP-420. In exploratory, non-GLP kidney toxicology studies, SP-420 displayed less kidney toxicity than other iron chelator drugs [deferitran, deferasirox], as assessed by the lack of measurable KIM-1 induction and the absence of changes in serum creatinine or blood urea nitrogen (BUN). In a first-in-human study conducted in healthy volunteers, single doses of SP-420 up to 13.2 mg/kg were well tolerated with dose-related PK and a plasma half-life (~9-17 hours) which supported either once daily (QD) or twice daily (BID) dosing (data on file).

Based on the promises from research in rats and the first-in-human study, the objectives of this study were to assess the safety, tolerability, and PK profile of SP-420 after multi-day dosing in transfusion-dependent β-thalassemia patients with iron overload.
Methods

Study Design and Patient Population

This was a phase Ib, dose-escalation study assessing SP-420 in β-thalassemia patients with chronic transfusional iron overload requiring treatment with an iron chelator. Patients were enrolled from study centers in Canada, Lebanon, Thailand and the United States from December 2014 through August 2015. This study was funded by Sideris Pharmaceuticals.

Eligible patients were followed for at least 6 months prior to screening in a specialized treatment center that maintained detailed medical records, including transfusion and iron chelation history. Patients were at least 18 years of age, weighed at least 35 kg, and had serum ferritin levels ≥700 ng/mL. Patients had a cardiac T2* score >20 ms within 12 months prior to the baseline visit or > 16 ms if cardiac T2* was assessed during the screening period, as long the score was stable or improving from prior scores. The protocol excluded patients who had hepatic dysfunction (defined as alanine aminotransferase level > 4 times the upper limit of normal), symptoms of cardiac dysfunction, symptoms of neuropathy, or clinically significant kidney disease (defined as serum creatinine > the upper limit of normal or urine protein to creatinine ratio > 0.5 mg/mg creatinine). The study also excluded patients with hepatitis B, hepatitis C, or HIV infection.

The study was performed in accordance with the Declaration of Helsinki, International Clinical Harmonization guidelines, Good Clinical Practice, and applicable regulatory requirements. Each study center obtained Institutional Review Board or Independent Ethics Committee approval to conduct the study before enrollment of patients. Informed consent was obtained from individual patients before any study specific procedures were conducted.

Treatment

Patients enrolled in the study discontinued their previous iron chelation therapy at least 7 days prior to the first dose of SP-420 and for the duration of the study. Six SP-420 dosing cohorts were sequentially evaluated for durations of 14 or 28 days. The SP-420 doses evaluated were 1.5 mg/kg once daily (QD) for 14 days, 3 mg/kg QD for 14 days, 6 mg/kg QD for 14 days, 12 mg/kg QD for 14 days, 24 mg/kg QD for 28 days, and 9 mg/kg twice daily (BID) for 28 days. Before sequential cohorts were dosed, the safety and available PK data from the preceding cohort(s) were first reviewed by a Clinical Safety Committee, consisting of the medical monitor, a clinical pharmacologist, and a
physician expert in the field who was not an investigator on the study. The study was initially designed to evaluate 48 mg/kg QD for 28 days in the final sixth cohort; however, after patients in the 24 mg/kg QD group experienced renal adverse events (described in the Safety section), the safety committee recommended a step-down dose of 9 mg/kg BID as the final dose to be evaluated. Patients were instructed to take their study drug on an empty stomach, defined as not having consumed a meal approximately 2 hours before and 1 hour after taking study drug. Patients were instructed to take their study drug at approximately the same time each day. Patients in the BID dosing cohort were instructed to take the study drug approximately 12 hours apart each day.

**Assessment**

Patients returned to the study center for weekly visits during treatment and were followed for seven days after study drug discontinuation so that post-treatment safety could be assessed. Safety was evaluated by assessment of adverse events (AE), performance of physical examinations, and evaluation of electrocardiograms (ECG) and clinical laboratory tests. Investigators assessed each AE for severity and relationship to study drug on a weekly basis. A serious adverse event (SAE) was defined as an AE that met any of the following: i) resulted in death, ii) was life-threatening, iii) required hospitalization, iv) resulted in persistent or significant disability/incapacity, or v) was an important medical event.

On day 7, serial blood samples were collected for PK analyses at the following time points: pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 10-12, and 24 hours post-dose. Plasma concentrations of SP-420 were quantitated using validated liquid chromatographic methods with mass-spectrometric detection (LC/MS/MS). The lower limit of quantitation for SP-420 was 10.0 ng/mL.

All patients who received at least one dose of study drug were included in the analysis. All data were summarized descriptively.
Results

Patient Disposition and Demographics

A total of 24 patients were enrolled in the study and received at least 1 dose of SP-420. Of the 24 patients dosed, 18 patients (75%) completed the treatment period. AEs were responsible for study drug discontinuation in one patient in the 24 mg/kg QD cohort (drug hypersensitivity reaction) and four patients in the 9 mg/kg BID cohort (drug hypersensitivity reaction, abdominal pain with nausea, abdominal distension, and acute kidney injury with proteinuria). The study was prematurely terminated by the sponsor due to renal adverse events (described in the Safety section) and thus a sixth patient who was receiving study drug at the time study of termination was also prematurely discontinued; this subject completed dosing through day 17.

Patient demographics are summarized in Table 1. In general, there was variability across each of the dosing cohorts, likely due to the small size of the study and thus the small number of patients in each dosing cohort. The mean age of patients across all cohorts was 28 years old, ranging from 18 to 56 years. Both male and female patients were well represented in the study. All the patients were either White or Asian.

Safety

18 of the 24 patients (75%) receiving study drug experienced an AE, with 7 of 12 (58%) patients in the lower dose 14-day cohorts and 11 of 12 (92%) patients in the higher-dose 28-day cohorts reporting events. The most commonly reported AEs are summarized in Table 2. Most were mild or moderate in intensity.

No deaths occurred during the study. Two SAEs were reported. One patient in the 24 mg/kg QD cohort was hospitalized with a generalized maculo-papular skin rash (drug hypersensitivity) approximately three weeks after initiating SP-420 treatment. The event was assessed as related to study drug and resolved upon SP-420 discontinuation and treatment with corticosteroids and antihistamines. Of note, one patient in the 9 mg/kg BID also discontinued study drug due to a drug hypersensitivity reaction, although this event was not considered serious. A second patient in the 9 mg/kg BID cohort was hospitalized seven days after completing treatment with SP-420 with an acute febrile illness of unknown etiology associated with acute hemolysis (assessed as not related to study drug). During the hospitalization, it was also observed that the patient had significant electrolyte imbalances, including hypokalemia, hypophosphatemia, and hypomagnesaemia, along with increased serum creatinine, proteinuria, and
glucosuria which led to a diagnosis of Fanconi syndrome. The patient was treated with intravenous fluids and electrolytes, and the event resolved. The Fanconi syndrome was assessed as related to the study drug.

In the higher-dose cohorts in which SP-420 was administered for 28 days, there were four patients who developed laboratory changes suggestive of renal dysfunction (one of these was the patient with the SAE of Fanconi syndrome, described above). After 14-21 days of dosing, these patients had a pattern of increasing serum creatinine (most with concurrent increases in blood urea nitrogen), proteinuria, elevation in urine protein/creatinine ratio, and glucosuria. Two of these patients had a doubling of serum creatinine levels, up to 2.0 mg/dL and an increase in urinary protein up to 6.24 g/L. All renal function abnormalities resolved upon discontinuation of study drug.

There were no clinically significant changes or patterns across cohorts in vital signs or ECG.

**Pharmacokinetics**

There was a near dose-linear increase in the mean ± standard error (SE) plasma SP-420 concentrations (Figure 1) and in the mean values for peak plasma concentration ($C_{\text{max}}$) and area under the curve (AUC) $AUC_{0-\tau}$ (Table 3) over the dose range evaluated. Any deviations from linearity are more likely explained by the small number of patients and the use of different patients (interpersonal variability) per cohort rather than to a true nonlinearity.

The median $t_{\text{max}}$ ranged from 0.5 to 2.25 h and was not dependent on dose (Table 3).

A summary of the day 7 plasma PK parameters for SP-420 is presented in Table 3. Day 7 mean SP-420 plasma concentrations are displayed in Figure 1.
Discussion

After multiple oral doses in transfusion-dependent β-thalassemia patients with iron overload, analysis of SP-420 plasma concentrations indicated near dose-linear PK over the dose range studied (1.5 mg/kg QD, 3 mg/kg QD, 6 mg/kg QD, 12 mg/kg QD, 24 mg/kg QD, and 9 mg/kg BID).

From a safety perspective, there were no observed safety signals after 14 days of exposure as doses were sequentially escalated through the 12 mg/kg QD cohort. In the 24 mg/kg QD cohort, in which SP-420 was administered for 28 days, individual patients developed reversible laboratory changes suggestive of renal dysfunction after 21 days of dosing. The findings included increasing serum creatinine and BUN, proteinuria, elevation in urine protein/creatinine ratio, and glucosuria. Based on these results from 24 mg/kg QD cohort, the Clinical Safety Committee decided against further dose escalation and recommended a step-down dose of 18 mg/kg (which was administered as 9 mg/kg BID) to be evaluated for 28 days. The same renal dysfunction was observed at the step-down dose, and, in some cases, manifested after 14 days of dosing. An increase in gastrointestinal disturbance was also seen. The renal function abnormalities and gastrointestinal disturbances resolved upon discontinuation of study drug. Based on these safety findings observed at 24 mg/kg QD and 9 mg/kg BID, the Sponsor terminated the study and discontinued development of SP-420. Plasma levels of SP-420, as measured by Cmax and AUC for the plasma concentration by time curve, were dose-related and dose-proportional over the range studied and generally comparable to the data from the previous study in healthy subjects. There was no evidence of drug accumulation.

This was a small, exploratory, early phase study, with relatively few patients included in each cohort. From the available data collected, there was no clear relationship between patient demographics, baseline characteristics and renal dysfunction. Similarly, there were no clear trends in day 7 study drug exposure (total or peak exposure) and renal function abnormalities. It is possible that total duration of treatment, i.e. cumulative exposure, played a role as toxicity was higher in the higher dose cohorts. These observed toxicities generally did not manifest until after 14-21 days of continuous dosing. Although no renal adverse effects were observed in the lower dose cohorts, these doses would have to be evaluated for longer durations to further assess their safety after continuous dosing and possible accumulation after long-term exposure.
Of note, one of the patients developed Fanconi syndrome that was deemed to be related to the study drug. Fanconi syndrome has been reported in the literature with the use of DFX.\textsuperscript{11-13} Although it is difficult to quantify the effect of SP-420 on glomerular filtration rate (GFR), the medication was associated with increased serum creatinine and, thus, a decreased estimated GFR. This AE has been also observed with DFX treatment.\textsuperscript{14} Incident proteinuria was observed in 20.8% of the patients treated with SP-420. The observed proteinuria was associated with higher doses of SP-420. DFX therapy was associated with proteinuria that was reversible upon temporary holding of treatment.\textsuperscript{15} Based on the renal findings in this clinical study, it would appear that the non-clinical results from the in vitro and animal studies were not predictive of toxicity in humans. In the GLP 28 day repeat-dose studies performed in the Sprague-Dawley (SD) rat, premature deaths of five animals (four non-iron-loaded and one iron-loaded) were observed in the high dose group (250 mg/kg). Renal tubular vacuolar degeneration was found in the non-iron-loaded rat. In the GLP 26-week chronic toxicity study in cohorts of iron-loaded and non-iron-loaded SD rats, all adverse findings were noted only in the high dose group at 90 mg/kg/day. Histopathological examination of specified tissues revealed segmental necrosis in the kidneys of two 90 mg/kg non-iron loaded males sacrificed at the end of the treatment period, and increased tubular basophilia in non-iron-loaded males and females at 90 mg/kg/day. These renal findings correlated with gross abnormalities and clinical pathology findings (increased urea and creatinine levels). Therefore, it is likely that iron overload might minimize renal toxicities from SP-420 similar to the effect seen in deferasirox; however, partly due to the small sample size, we did not find any correlation between baseline iron overload in our patients and renal toxicity protection in this study. Interestingly, it has been hypothesized that the underlying mechanism of renal toxicity of iron chelators may not be related to a nephrotoxic effect of the iron chelator drug itself but to overchelation leading to a relative depletion of iron and a subsequent reduction in GFR.\textsuperscript{16} Thus, it is possible that highly efficient iron chelators, as a function of their efficacy, may be depleting the necessary and natural pools of iron within the renal tubular cells, resulting in toxicity. The iron chelating efficacy for SP-420 compared to deferasirox after oral dosing was 26.7±4.7% (300 µmol/kg) versus 14.6± 4% (268 µmol/kg) and 26.3±9.9 (75 µmol/kg) versus 29% (150 µmol/kg) in rats and monkeys, respectively.\textsuperscript{8} Moreover, it has been suggested that iron excretion with SP-420 was approximately dose-proportional throughout the dose range of 50 to 300 µmol/kg with absolute iron excretion increasing 7.7-fold over the 6-fold dose range without ‘dose flattening’ commonly observed in other iron chelators. Consequently, it is possible that lower doses of a very efficient iron chelator may be safe and still have clinical benefit for patients. Also, in this study and with the related molecule,
deferitrin, more frequent dosing (i.e., BID) resulted in greater toxicity as compared with QD dosing. SP-420, unlike other chelators, has prolonged iron excretion (~48 hours) following a single-dose in the bile duct-cannulated rat model, and therefore has the potential to be effective if dosed every other day. This would minimize renal tubular cell exposure and perhaps allow for higher doses to be safely administered. Because long term efficacy was not assessed in this short-term safety and PK study, additional studies assessing efficacy and safety of lower doses or less frequent dosing (i.e., every other day dosing) over longer durations would be necessary to address this question adequately. Extrapolating from animal studies to projected human exposure, the nonclinical efficacy studies would suggest that clinical doses of 20 to 100 mg/kg/day may be associated with significant iron clearance in humans, assuming similar PK and iron clearance efficiency across species. The safety signal at the doses used ended the development of this compound as the predicted dosing to achieve meaningful iron removal was higher than the predicted maximum tolerated dose. Different schedules were modeled without being able to achieve adequate exposure without inducing renal toxicity. As a conclusion, the authors believe that publishing studies that have yielded negative results is invaluable to a field that is focused on promoting advancement while learning from previous clinical experiences. Moreover, as one of the ‘rare’ disease conditions in developed world, our clinical information in patients with β thalassemia would be useful for developing future iron chelators of this class or others and guiding new drug design.
Conflicts of interest

ATT reports receiving honoraria and research funding from Novartis Pharmaceuticals and research funding from Celgene.

ANS has no conflicts of interest to disclose.

KHK is a consultant for Agios, Alexion, Celgene, and Novartis; a member of the scientific advisory board for Agios and Novartis; receives honoraria from Alexion and Novartis; and receives research funding as a co-investigator from Agios, Alexion, Celgene, and Novartis.

ARC is a consultant for Novartis and Roche, and is a member of the DMSB for two studies sponsored by ApoPharma.

EJN has served as a consultant for Novartis. He is a member of a DSMB for ApoPharma, and has been a member of ApoPharma advisory boards. His institution has received research funds from Shire and Novartis.

YA has served as membership on advisory committees for Novartis. Her institution has received research funds from Novartis, Cerus, Shire and Celgene.

JLK is a consultant for Agios and Ionis Pharmaceuticals and has received research funding as a co-investigator from Novartis Pharmaceuticals Corporation, Agios Pharmaceuticals, Apopharma, Inc, and Bluebird Bio.

BJJ and KP were employees in Sideris at the time of the study.

GB was employee, officer, and shareholder in Sideris at the time of the study.

VV is a consultant for Novartis, Roche, Celgene, Agios, and Ionis Pharmaceuticals and has received research funding as a principle and co-investigator from Novartis Pharmaceuticals Corporation, Roche Pharmaceuticals Corporation, Celgene Pharmaceuticals Corporation, Biorad Co. Ltd. and SEBIA Co. Ltd.
Authorship contributions

Study conception, design, and implementation: ATT, ANS, KHK, ARC, EJN, YA, JLK, GB, BJ, KP, VV

Manuscript preparation: ANS, ATT, VV

Manuscript review: ANS, ATT, KHK, ARC, EJN, YA, JLK, GB, VV
Acknowledgements

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References

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<tr>
<th></th>
<th>1.5 mg/kg</th>
<th>3 mg/kg</th>
<th>6 mg/kg</th>
<th>12 mg/kg</th>
<th>24 mg/kg</th>
<th>9 mg/kg</th>
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<tr>
<td>QD x 14 days (N=3)</td>
<td>QD x 14 days (N=3)</td>
<td>QD x 14 days (N=3)</td>
<td>QD x 14 days (N=3)</td>
<td>QD x 28 days (N=6)</td>
<td>QD x 28 days (N=6)</td>
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</tr>
<tr>
<td>Age, mean years (range)</td>
<td>42 (37-45)</td>
<td>36 (22-56)</td>
<td>21 (18-24)</td>
<td>26 (21-31)</td>
<td>19 (18-21)</td>
<td>31 (19-46)</td>
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<td>Gender, n</td>
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<td>Race, n</td>
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<td>Baseline serum ferritin (ng/mL), median (range)</td>
<td>1413 (1198-2091)</td>
<td>1169 (839-2597)</td>
<td>1852 (1073-4481)</td>
<td>1605 (1363-5967)</td>
<td>2496 (1384-5892)</td>
<td>2796 (669-4425)</td>
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### Table 2: Adverse Events

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<tr>
<th>Condition</th>
<th>1.5 mg/kg QD x 14 days (N=3)</th>
<th>3 mg/kg QD x 14 days (N=3)</th>
<th>6 mg/kg QD x 14 days (N=3)</th>
<th>12 mg/kg QD x 14 days (N=3)</th>
<th>24 mg/kg QD x 28 days (N=6)</th>
<th>9 mg/kg BID x 28 days (N=6)</th>
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<tr>
<td>Gastrointestinal disturbances</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
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<td>6</td>
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<td>Acute kidney injury</td>
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<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Elevated transaminase (ALT or AST)</td>
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<td>0</td>
<td>0</td>
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<td>Arthralgia</td>
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<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Drug hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Fanconi syndrome</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
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<td>Hemolysis</td>
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<td>0</td>
<td>0</td>
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<td>Rash maculo-papular</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Thrombocytopenia</td>
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Table 3: Plasma PK parameters of SP-420 at day 7

<table>
<thead>
<tr>
<th>Dose (mg/kg) / Frequency</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-τ&lt;/sub&gt; (h x ng/mL)*</th>
<th>CL/F (L/h/kg)</th>
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<tr>
<td>1.5/QD</td>
<td>4,933 ± 2,039 (3)</td>
<td>0.50 (3) [0.25-0.57]</td>
<td>13,810 ± 2,374 (3)</td>
<td>0.118 ± 0.020 (3)</td>
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<tr>
<td>3/QD</td>
<td>9,900 ± 10,324 (2*)</td>
<td>2.25 (2*) [0.50-4.00]</td>
<td>28,690 ± 15,555 (2*)</td>
<td>0.097 ± 0.025 (2*)</td>
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<tr>
<td>6/QD</td>
<td>11,987 ± 8,090 (3)</td>
<td>1.00 (3) [0.25-2.00]</td>
<td>32,117 ± 12,434 (3)</td>
<td>0.228 ± 0.077 (3)</td>
</tr>
<tr>
<td>12/QD</td>
<td>25,633 ± 12,083 (3)</td>
<td>1.00 (3) [0.51-2.00]</td>
<td>84,056 ± 29,494 (3)</td>
<td>0.149 ± 0.045 (3)</td>
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<tr>
<td>24/QD</td>
<td>46,767 ± 38,515 (6)</td>
<td>1.50 (6) [1.00-2.03]</td>
<td>151,446 ± 103,753 (6)</td>
<td>0.202 ± 0.088 (6)</td>
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<tr>
<td>9/BID</td>
<td>23,450 ± 14,531 (6)</td>
<td>1.00 (6) [0.50-2.00]</td>
<td>81,642 ± 54,002 (6)</td>
<td>0.137 ± 0.055 (6)</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD (N), except for T<sub>max</sub> where median (N) [range] is reported.

*AUC<sub>0-τ</sub> is to 24 hours for QD administration and to 12 hours for BID administration.

*1 patient excluded from PK analysis for missing 2 doses.
Mean ± standard error plasma SP-420 concentrations at Day 7

130x86mm (144 x 144 DPI)