Intravenous Pharmacokinetics, Local Tolerability, and Hemolysis of an SBE7-β-Cyclodextrin Formulation of the Neurokinin-1 Receptor Antagonist Vestipitant

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Abstract

Vestipitant is a potent and selective neurokinin 1 (NK-1) receptor antagonist that was investigated as a potential treatment for post-operative nausea and vomiting (PONV). A previous mannitol-based formulation of vestipitant was associated with hemolytic activity in preclinical studies. In an effort to reduce the hemolytic potential and develop an IV formulation of vestipitant that could be administered more rapidly, an IV formulation containing sulfobutylether-7-beta-cyclodextrin (SBE7-β-CD, Captisol™) was developed and tested in a phase 1 clinical study. This was a randomized, single-blind (subjects and investigator—blinded, sponsor—unblinded), placebo controlled, dose escalation study in healthy subjects in which 7 cohorts of 8 subjects per cohort received SBE7-β-CD-based vestipitant (2 mg/mL) or placebo (saline) in a 3:1 ratio (active:placebo) at different doses and infusion rates. The results demonstrated the ability to infuse up to 48 mg vestipitant in a 2 mg/mL formulation over 30 seconds with no evidence of hemolytic effects. Cohorts of subjects at lower doses and longer infusion duration (>1 minute) reported more AEs related to the infusion site than those at the higher doses and faster infusion rates.

Keywords

NK-1 receptor antagonist, vestipitant, SBE7-β-cyclodextrin, hemolysis, intravenous

Vestipitant is a potent and selective neurokinin 1 (NK-1) receptor antagonist that was being investigated as a potential treatment for post-operative nausea and vomiting (PONV) and has been evaluated for other indications including depression, anxiety, chemotherapy-induced nausea and vomiting, tinnitus, and primary insomnia.¹⁻³

Preclinical studies with a mannitol-based intravenous (IV) formulation of vestipitant, demonstrated the potential for hemolysis and injection site irritation when administered at concentrations greater than 0.2 mg/mL. Thus, in order to avoid local tolerability and hemolysis effects, IV vestipitant was administered to human subjects as a 15-minute-infusion at concentrations not greater than 0.1 mg/mL. Other NK-1 inhibitors, such as fosaprepitant dimeglumine,⁴ have similar infusion rate restrictions; therefore a more rapid administration would provide more treatment flexibility.

In an effort to reduce the hemolytic potential and develop an IV formulation of vestipitant that could be administered more rapidly, an IV formulation containing sulfobutylether-7-beta-cyclodextrin (SBE7-β-CD, Captisol™) was developed. The SBE7-β-CD formulation of IV vestipitant did not demonstrate any local tolerability findings when given in a single-dose...
study in dogs up to the maximum concentration (4 mg/mL) administered compared to irritation and hemolysis observed with a mannitol formulation at 1 and 2 mg/mL, respectively. Consistently, in vitro studies indicated that up to 2 mg/mL vestipitant in a SBE7-β-CD formulation mixed with human blood did not produce hemolysis. The purpose for the current study was to evaluate the safety and tolerability and pharmacokinetics (PK) of the SBE7-β-CD formulation of vestipitant when administered over 2 minutes or less to healthy subjects.

Materials and Methods

Study Design and Participants
This study was conducted in Australia (Nucleus Network, Melbourne, Australia) according to the ethical principles of “good clinical practice” (GCP) and the Declaration of Helsinki after obtaining a written informed consent from each subject. The protocol and its amendment were approved by the Alfred Hospital Ethics Committee (Melbourne, Australia).

This was a randomized, single-blind (subjects and investigator), placebo controlled, dose escalation study in healthy subjects (ClinTrials.gov identifier: NCT01290133). The sponsor was unblinded to study treatment. The study planned to enroll eight subjects into each of seven cohorts, such that six subjects would be randomized to receive the SBE7-β-CD-based vestipitant (2 mg/mL) formulation and two subjects would receive placebo (saline injection). Each subject participated in only one cohort. Each cohort consisted of three periods for all subjects (screening, treatment, and follow-up). Safety and PK were assessed throughout the study. The doses of vestipitant and regimen designations for this study are summarized in Table 1.

Pharmacokinetic Assessments
Blood samples for PK analysis were collected at predose (0), end of infusion, 5, 30 minutes, and 1, 1.5, 2, 4, 6, 10, 18, 24, and 36 hours post dose. Concentrations of vestipitant in human plasma were determined using a high-performance liquid chromatography (HPLC) assay coupled with a triple quadruple mass spectrometer with an electrospray ionisation interface. $[^2H_3^{13}C]$-vestipitant

| Table 1. Doses and Administration Rates |
|----------------------------------------|
| Cohort | n | Vestipitant dose | Solution volume (mL) | Infusion time (minutes) | Treatment infusion rate | Solution infusion rate (mL/min) |
|        |   |                  |                      |                        |                          |                                |
| 1       | 2 | Placebo          | 6                    | 2                      | —                        | 3                               |
|         | 6 | 12 mg            | 6                    | —                      | 6 mg/min                 | 3                               |
| 2       | 2 | Placebo          | 9                    | 2                      | —                        | 4.5                             |
|         | 5 | 18 mg            | 9                    | 2                      | 9 mg/min                 | 4.5                             |
| 3       | 2 | Placebo          | 12                   | 2                      | —                        | 6                               |
|         | 6 | 24 mg            | 12                   | 2                      | 12 mg/min                | 6                               |
| 4       | 2 | Placebo          | 12                   | 1                      | —                        | 12                              |
|         | 6 | 24 mg            | 12                   | 1                      | 24 mg/min                | 12                              |
| 5       | 2 | Placebo          | 12                   | 0.5                    | —                        | 24                              |
|         | 6 | 24 mg            | 12                   | 0.5                    | 48 mg/min                | 24                              |
| 6       | 2 | Placebo          | 18                   | 0.5                    | —                        | 36                              |
|         | 6 | 36 mg            | 18                   | 0.5                    | 72 mg/min                | 36                              |
| 7       | 2 | Placebo          | 24                   | 0.5                    | —                        | 48                              |
|         | 6 | 48 mg            | 24                   | 0.5                    | 96 mg/min                | 48                              |
Cmax (tmax), area under the plasma concentration-time curve (AUC0–1), and maximum observed plasma concentration (Cmax) were measured. In the placebo group, 3 of 3 subjects had infusion site findings within the first 30 minutes of infusion. The majority of findings, 57% of the total, were generally related to bruising and were observed in the placebo and vestipitant groups. 89% of the subjects receiving vestipitant experienced at least one Grade 1 finding; thus, dose escalation to the next highest cohort proceeded as planned. The majority of events associated with infusion site conditions were considered related to the study medication by the investigator. There were no serious AEs, deaths, or withdrawals due to AEs during this study. There were no clinically significant findings in clinical laboratory tests (chemistry, hematology, urinalysis), vital signs or ECGs in this study, and no apparent dose-related trends.

Statistical Analyses
The primary objectives of this study were to describe the safety and tolerability in healthy subjects following single IV infusions of the SBE7-β-CD-based vestipitant formulation. The secondary objectives were to characterize the PK and dose proportionality of the SBE7-β-CD-based vestipitant formulation in healthy subjects. For all safety data, summaries of actual value and changes from baseline in the following parameters were generated: vital signs (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and pulse rate), ECG values (ventricular rate, intervals of PR, QRS, QT, and QTe), clinical chemistry, and hematology values.

From the plasma concentration–time data, the following PK parameters were determined, as data permitted: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC0–1), apparent terminal phase half-life (t½), total plasma clearance (CL) volume of distribution at steady-state (Vdss), and volume of distribution based on the terminal phase (Vz). Dose proportionality of AUC0–1 and Cmax (30 seconds and 2 minutes infusion cohorts separately) for vestipitant were assessed using the following power model: log(PK parameter) = a + b × log(dose), where a is the intercept and b is the slope. The mean slope was estimated from the power model and the corresponding 90% confidence interval calculated.

Results
Demographics
A total of 55 healthy subjects were randomized into the study across 7 cohorts, in which 14 subjects received placebo and a total of 41 subjects received the SBE7-β-CD-based vestipitant formulation. Subjects were generally well-matched between the placebo and the combined vestipitant doses with respect to age, gender, and race. The majority of subjects in both groups were White/Caucasian males.

Safety
The overall frequency of reported AEs was similar between the saline placebo (57%) and the combined vestipitant groups (56%) as summarized in Table 2. The most commonly reported AEs in ≥2 subjects, regardless of the dose of vestipitant received, were infusion site pain, infusion related reaction, infusion site hematoma, infusion site discomfort, headache, lethargy, procedural dizziness, dysgeusia, myalgia, and upper respiratory tract infection (Table 2). The majority of events associated with infusion site conditions were considered related to the study medication by the investigator. All AEs were mild, except for one case of moderate headache in a subject that received vestipitant 12 mg, which was considered related to the study medication.

There were no serious AEs, deaths, or withdrawals due to AEs during this study. There were no clinically significant findings in clinical laboratory tests (chemistry, hematology, urinalysis), vital signs or ECGs in this study, and no apparent dose-related trends.
findings in the placebo group and only one finding in the vestipitant group.

Female subjects reported AEs at a higher overall rate (90%, 18 of 20) than males (37%, 13 of 35), regardless of treatment assignment or dose. However, no female subjects were recruited into the 30-second infusion cohorts. In the 1 and 2 minute infusion placebo groups, 2 of 5 females (40%) and 1 of 3 males (33%) had findings. In the 1 and 2 minute infusion vestipitant groups, 11 of 15 females (73%) and 2 of 8 males (25%) had findings (Table 3).

Table 2. Summary of Adverse Events Reported in ≥2 Subjects, Regardless of Causality

| Preferred term, n (%) | Total (N = 55) | Placebo (N = 14) | Vestipitant cohort |
|-----------------------|---------------|------------------|-------------------|
|                       |               |                  | 1 (N = 6) | 2 (N = 5) | 3 (N = 6) | 4 (N = 6) | 5 (N = 6) | 6 (N = 6) | 7 (N = 6) |
| Infusion time         |               |                  | 12 mg/2 min | 18 mg/2 min | 24 mg/2 min | 24 mg/1 min | 24 mg/30 s | 36 mg/30 s | 48 mg/30 s |
| Subjects with any AE  | 31 (56)       | 8 (57)           | 5 (83)      | 5 (100)     | 4 (67)      | 3 (50)      | 1 (17)     | 3 (50)     | 2 (33)     |
| Subject with any related AE | 25 (45) | 6 (43)           | 4 (67)      | 5 (100)     | 4 (67)      | 2 (33)      | 1 (17)     | 1 (17)     | 0          |
| Infusion site pain    | 5 (9)         | 0                | 1 (17)      | 1 (20)      | 2 (33)      | 1 (17)      | 0          | 0          | 0          |
| Infusion related reaction | 5 (9) | 0                | 3 (50)      | 1 (20)      | 0          | 0          | 0          | 0          | 1 (17)     |
| Infusion site hematoma| 5 (9)         | 2 (14)           | 0           | 1 (20)      | 2 (33)      | 0          | 0          | 0          | 0          |
| Headache              | 5 (9)         | 1 (7)            | 1 (17)      | 1 (20)      | 1 (17)      | 1 (17)      | 0          | 0          | 0          |
| Lethargy              | 4 (7)         | 0                | 0           | 2 (40)      | 0          | 0          | 0          | 0          | 2 (33)     |
| Procedural dizziness  | 3 (5)         | 0                | 1 (17)      | 1 (20)      | 0          | 1 (17)      | 0          | 0          | 0          |
| Somnolence            | 3 (5)         | 2 (14)           | 0           | 0           | 0          | 0          | 1 (17)     | 0          | 0          |
| Dysgeusia             | 2 (4)         | 0                | 0           | 0           | 0           | 1 (17)      | 1 (17)     | 0          | 0          |
| Infusion site discomfort | 2 (4) | 0                | 0           | 0           | 0           | 1 (17)      | 0          | 1 (17)     | 0          |
| Myalgia               | 2 (4)         | 0                | 1 (17)      | 0           | 0           | 1 (17)      | 0          | 0          | 0          |
| Upper respiratory tract infection | 2 (4) | 0                | 2 (33)      | 0           | 0           | 0          | 0          | 0          | 0          |
| Abdominal pain        | 2 (4)         | 1 (7)            | 0           | 0           | 0           | 1 (17)      | 0          | 0          | 0          |

Hemolysis
Overall, there was no pattern in the data indicative of potential hemolysis, either individually or by treatment. The average changes from baseline in parameters of hemolysis were variable in the vestipitant treatment groups, with some regimens having a decrease and some with an increase in a non-dose dependent manner. However, all average changes were well within the expected sample variability of 0.1 g/L and less than the decrease observed after footstrike hemolysis.

Table 3. Number of Subjects (by Cohort) with ≥1 Grade 1 Infusion Site Finding

| Dose/infusion time | 1 2 3 4 5 6 7 Total (%) |
|--------------------|-------------------------|
| Placebo (N = 2 each) |
| Female             | 1 of 2                  | 1 of 2      | 0 of 2      | 1 of 2      | 0 of 2      | 0 of 2      | 3 of 2      | 3 of 4 (21%) |
| Male               | NA                      | NA          | 0 of 1      | NA          | NA          | NA          | 2 of 1      | 2 of 5 (40%) |
| Vestipitant (N = 6 each) |
| Female             | 4 of 4                  | 4 of 5      | 3 of 6      | 2 of 6      | 0 of 6      | 1 of 6      | 14 of 6     | 14 of 7 (34%) |
| Male               | 0 of 2                  | NA          | 2 of 4      | 0 of 2      | 0 of 6      | 1 of 6      | 0 of 6      | 3 of 7 (12%) |

NA, not applicable.

aAll Infusion Site Findings were Grade 1—no Grade 2 or Grade 3.

bIncludes 1 subject whose findings were also observed pre-dose.

Only 5 subjects received vestipitant in Cohort 2.
(0.085 g/L decrease)\(^6\) and generally similar to placebo subjects.

One placebo subject had an infusion site hematoma. Laboratory findings were consistent with evidence of hemolysis and included a 0.20 g/L decrease in haptoglobin, a 121 U/L increase in LDH, and a 1 mmol/L increase in potassium (end of infusion sample).

**Pharmacokinetics**

Pharmacokinetic profiles and parameters are summarized in Figure 1 and Table 4, respectively. Peak plasma vestipitant concentrations (C\(_{\text{max}}\)) were generally observed in the end of infusion sample for treatment groups that received the SBE7-β-CD-based vestipitant formulation over 2 minutes (12, 18, and 24 mg), although it was highly variable. As infusion duration was reduced, t\(_{\text{max}}\) was delayed slightly, and C\(_{\text{max}}\) was frequently observed in the PK sample obtained subsequent to the end of infusion PK sample. When vestipitant was infused over 30 seconds (24, 36, and 48 mg), median t\(_{\text{max}}\) values of 4.8–5.4 minutes were observed. Accordingly, the observed C\(_{\text{max}}\) was variable and inconsistent between cohorts.

There were greater than dose proportional increases in AUC\(_{0-\infty}\) for plasma vestipitant over the dose range studied, with a slope estimate from the power model of 1.33 (90% CI: 1.12, 1.53), where 1.00 would represent dose-proportional increases. Dose proportionality assessment of C\(_{\text{max}}\) could not be reliably assessed due to the highly variable estimates described above.

**Discussion**

Several NK-1 receptor antagonists have been demonstrated to be effective for the treatment of PONV and chemotherapy-induced nausea and vomiting (CINV).\(^7\)–\(^9\) Approved medications are available as oral and IV formulations. Fosaprepitant dimeglumine must be infused over 20–30 minutes (single dose regimen) or over 15 minutes (3-day regimen) for CINV, and cannot be administered as a bolus infusion.\(^4\) Vestipitant has been in development as an oral agent for many indications including PONV and CINV. An IV formulation (mannitol based) was created to provide better flexibility for use in patients in settings where oral administration is contraindicated or not tolerated. However, this formulation could only be administered by a slow (15 minutes) infusion at concentrations not greater than 0.1 mg/mL to avoid any potential risk of hemolysis. Preclinical data demonstrated the potential for hemolysis or local irritation when administered at concentrations greater than 0.2 mg/mL. While the infusion duration of this mannitol-based vestipitant formulation was similar to that for fosaprepitant,\(^4\) the goal was to develop a formulation allowing for much more rapid (bolus) infusion while minimizing infusion site reactions and eliminate the potential for hemolysis. Such a formulation is more adapted to acute setting of PONV such as rescue treatment post-surgery.

To achieve this goal, a new formulation of vestipitant was developed using SBE7-β-CD. It is hypothesized that the use of SBE7-β-CD in the vestipitant formulation...
Table 4. Summary of Key Pharmacokinetic Parameters after Single Dose IV Infusion of the Captisol™-based Vestipitant Formulation

| Vestipitant dose | Nominal infusion time (minutes) | Solution volume (mL) | N | AUC_{0-\infty}^a (ng·h/mL) | C_{max}^a (ng/mL) | t_{max}^b (h) | t_{1/2}^a (h) | CL^a (L/h) | Vdss^a (L) | Vz^a (L) |
|----------------|-------------------------------|---------------------|---|---------------------------|----------------|-------------|-------------|-------------|-------------|---------|
| 12 mg          | 2                             | 6                   | 6 | 488 (33.3)                | 192 (68.5)    | 0.03 (0.00–0.05) | 8.52 (39.2) | 24.6 (33.3) | 267 (27.6) | 302 (23.4) |
|                |                               |                     |   | [510 ± 166.7]             | [219 ± 104.9] |             |             |             |             |         |
| 18 mg          | 2                             | 9                   | 6 | 689 (24.8)                | 382 (59.7)    | 0.03 (0.00–0.03) | 7.25 (18.6) | 26.1 (24.8) | 236 (20.0) | 317 (11.7) |
|                |                               |                     |   | [705 ± 168.2]             | [424 ± 186.3] |             |             |             |             |         |
| 24 mg          | 2                             | 12                  | 6 | 1,042 (18.7)              | 1,131 (104.0) | 0.03 (0.00–0.00) | 9.84 (24.0) | 17.1 (18.7) | 194 (19.0) | 273 (30.3) |
|                |                               |                     |   | [1,422 ± 255.8]           | [1,454 ± 991.0] |             |             |             |             |         |
| 24 mg          | 1                             | 12                  | 6 | 974 (34.1)                | 152 (103.3)   | 0.26 (0.02–0.50) | 7.74 (23.1) | 24.5 (34.9) | 262 (35.1) | 243 (15.2) |
|                |                               |                     |   | [1,022 ± 367.9]           | [225 ± 770.5] |             |             |             |             |         |
| 24 mg          | 0.5                           | 12                  | 6 | 1,045 (31.5)              | 372 (47.0)    | 0.08 (0.00–0.09) | 10.2 (34.8) | 23.0 (31.5) | 303 (22.1) | 339 (19.7) |
|                |                               |                     |   | [1,088 ± 340.1]           | [407 ± 200.0] |             |             |             |             |         |
| 36 mg          | 0.5                           | 18                  | 6 | 1,982 (50.0)              | 449 (31.4)    | 0.08 (0.00–0.08) | 13.1 (35.2) | 180 (52.1)  | 315 (21.8) | 340 (24.1) |
|                |                               |                     |   | [2,185 ± 1113.4]          | [466 ± 137.3] |             |             |             |             |         |
| 48 mg          | 0.5                           | 24                  | 6 | 2,928 (25.8)              | 581 (41.1)    | 0.09 (0.00–0.10) | 13.6 (19.6) | 16.4 (25.8) | 284 (20.2) | 322 (25)  |
|                |                               |                     |   | [3,001 ± 668.7]           | [622 ± 262.3] |             |             |             |             |         |

aGeometric mean (%CV) [arithmetic mean ± SD].
bMedian (min–max), [arithmetic mean ± SD].
hemolytic effects. For our clinical study evaluating the SBE7-β-CD-based formulation of vestipitant, haptoglobin levels were examined along with other laboratory and clinical evaluations for hemolysis. Only one subject who had received placebo (saline) exhibited laboratory changes indicative of hemolysis. In this case, haptoglobin levels decreased by 0.20 g/L, which was the second largest decrease observed in any subject in the study and was of a greater magnitude than the expected within-subject variability of 0.1 g/L, as noted. Although at least one decrease from baseline >0.1 g/L was observed in 3/14 (21%) placebo subjects and 9/34 (26%) vestipitant subjects, only the one placebo subject with the decrease by 0.20 g/L also had a 121 U/L increase in LDH and a 1 mmol/L increase in potassium along with observation of a hematoma at the infusion site, consistent with hemolysis.

Single dose administration of the SBE7-β-CD-based formulation of IV vestipitant (2 mg/mL) resulted in greater than dose proportional increases in AUC, an observation consistent with the increases in half-life and reductions in clearance observed with increasing dose. While variable between cohorts, Vdss is generally consistent across the dose range studied, suggesting this parameter is unlikely to be responsible for the greater-than-dose-proportional AUC observed. Plasma Cmax and tmax was highly variable in this study, most likely a result of the inherent variation in obtaining a PK sample soon after a rapid IV infusion of a drug that distributes rapidly. The highly variable plasma concentrations in the end of infusion PK sample (which did not always reflect the tmax/Cmax), also may reflect inadequate mixing of vestipitant in the plasma compartment immediately after the infusion. The effects of dose and infusion duration on vestipitant PK are confounded in this study, and with the exception of impacting Cmax, infusion duration does not appear to have a significant impact on the disposition of vestipitant.

In summary, the results of this study demonstrated that a SBE7-β-CD formulation of vestipitant allowed for a rapid infusion of this NK-1 antagonist with no evidence of hemolytic effects.

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Declaration of Conflicting Interests

All authors, except for P.H., are employees of GlaxoSmithKline. P.H. was the principal investigator of the study involved with the study conduct. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. Editorial support (development of the first draft, assembling tables and figures, collating author comments, and referencing) was provided by Guissou Dabiri, PhD, and was funded by GSK.

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