Poster CT14

Bioequivalence of HTX-019 (Aprepitant IV) and Fosaprepitant in Healthy Subjects

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BACKGROUND

Chemotherapy-Induced Nausea and Vomiting (CINV)

- Suboptimal control of CINV following moderately or highly emetogenic chemotherapy remains a significant challenge, particularly in the delayed phase (24-120 h after chemotherapy)[1,2]
- CINV can have profound negative effects on quality of life, even leading to chemotherapy dose reductions or delays[1]

CINV Prophylaxis and Unmet Need

- The consensus guideline-recommended treatment regimen for CINV control following emetogenic chemotherapy comprises a 3-drug regimen of a 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist (RA) + dexamethasone + a neurokinin 1 (NK-1) RA[3-6]
- Aprepitant, an NK-1 RA used for CINV prophylaxis, is available only in an oral formulation (EMEND PO) due to its low water solubility[7,8]
- Fosaprepitant, an IV aprepitant prodrug (EMEND IV),[9] was developed to provide a more convenient route of administration; however,
  - It has been associated with hypersensitivity and infusion-site reactions, primarily attributed to its surfactant, polysorbate 80[10]
    - Hypersensitivity reactions associated with fosaprepitant IV include pain, erythema, swelling, induration, and thrombophlebitis[11]

RATIONALE AND OBJECTIVES

- A surfactant-free IV formulation of aprepitant may provide patients with a safer NK-1 RA option with a lower risk of hypersensitivity and infusion-site reactions
- The primary objective of this study was to determine the bioequivalence of a surfactant-free aprepitant IV (HTX-019) and fosaprepitant (EMEND IV) in healthy subjects
  - The secondary objective was to evaluate safety and tolerability of HTX-019 IV and fosaprepitant IV in healthy subjects

METHODS

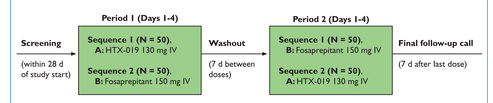
Main Eligibility Criteria

- Healthy men or women aged 18-55 years
- ≥ 50 kg body weight; body mass index between 18 and 35 kg/m^2
- Not pregnant or breastfeeding

Study Design

- This study was a phase 1, open-label, randomized, 2-way crossover evaluation of HTX-019 and fosaprepitant bioequivalence, each agent administered as a single IV dose in healthy subjects (**Figure 1**)
- Subjects received HTX-019 130 mg or fosaprepitant 150 mg, administered IV over 30 minutes on day 1 of periods 1 and 2 in a crossover fashion (**Figure 1**)

Figure 1. Phase 1 Study Design



- **Observation period duration was 72 hours for each treatment period**

Note: Confinement lasted from the morning of day –1 through day 4 of each treatment period (through the pharmacokinetic collection at 72 h on day 4), for a total of approximately 5 days per treatment period.

Pharmacokinetic (PK) Assessments

- Blood samples for measurement of aprepitant PK analysis were collected before dosing and at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 11, 12, 18, 24, 36, 48, 60, and 72 hours after infusion start in each treatment period
  - Additional samples for fosaprepitant were collected before dosing and at 0.5, 0.75, 1, and 1.5 hours after infusion start
- Plasma concentrations were determined using validated liquid chromatography/mass spectrometry
- Bioequivalence evaluation using a mixed-effects model was based on aprepitant area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable plasma concentration (AUC_{0-t}), from time 0 extrapolated to infinity (AUC_{0-inf}), and postequilibrium plasma aprepitant concentrations at 12 hours (C_{12h})
  - Bioequivalence was declared if 90% CI was within 80% to 125%

Safety Assessments

- Safety evaluations included treatment-emergent adverse events (TEAEs), serious adverse events, clinical laboratory results, vital signs, and ECGs
- An analysis was done of TEAE rate per subject-day using a negative binomial regression model

RESULTS

Subjects

- 100 healthy adult subjects were enrolled
- Demographics and baseline characteristics were comparable between the 2 treatment sequences (**Table 1**)

Table 1. Demographics and Baseline Clinical Characteristics (Safety Population)

	Sequence 1: AB N = 50	Sequence 2: BA N = 50	Overall N = 100
Age, mean (SD), y	38 (10)	33 (9)	35 (10)
Weight, mean (SD), kg	77 (13)	79 (15)	78 (14)
Height, mean (SD), cm	170 (9)	172 (10)	171 (10)
Body mass index, mean (SD), kg/m^2	27 (3)	27 (4)	27 (4)
Sex, n (%)			
Female	18 (36)	18 (36)	36 (36)
Male	32 (64)	32 (64)	64 (64)
Race, white, n (%)	30 (60)	25 (50)	55 (55)
Ethnicity, n (%)			
Not Hispanic or Latino	47 (94)	41 (82)	88 (88)

Note: Treatment A, HTX-019 130 mg IV; treatment B, fosaprepitant 150 mg IV.
SD = standard deviation.

- Among the 100 subjects enrolled, 97 (97%) completed the study and were included in the PK analysis
  - 3 subjects discontinued the study, 2 because of adverse events and 1 because of protocol deviation
- 100 subjects received at least 1 dose of study drug and were included in the safety analysis

Pharmacokinetics

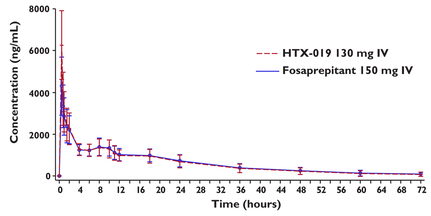
Plasma Fosaprepitant Concentrations After IV Administration of Fosaprepitant

- Rapid fosaprepitant-to-aprepitant conversion was confirmed, with no fosaprepitant detected in plasma at 0.75 hours
  - The mean maximum concentration (C_{max}) of fosaprepitant was 4446 ng/mL at 0.5 hours (end of infusion)

Aprepitant Plasma Concentrations After IV Administration of HTX-019 and Fosaprepitant

- Plasma concentrations of aprepitant over time after administration of HTX-019 and fosaprepitant are shown in **Figure 2**

Figure 2. Mean Plasma Aprepitant Concentrations Over Time (PK Population)



PK = pharmacokinetics.

- For HTX-019, the mean (CV%) C_{max} for aprepitant was 6265 (26.2%) ng/mL at a median time of C_{max} (T_{max}) of 0.5 hours
- For fosaprepitant, the mean (CV%) C_{max} for aprepitant was 4303 (32.3%) ng/mL at a median T_{max} of 0.5 hours
- Mean AUC_{0-t}, AUC_{0-inf}, and C_{12h} values for aprepitant after HTX-019 and fosaprepitant administration are shown in **Table 2**

Table 2. AUC_{0-t}, AUC_{0-inf}, and C_{12h} for Aprepitant After IV Administration of HTX-019 and Fosaprepitant (PK Population)

		Mean (CV%)	
PK Parameter	N	HTX-019 130 mg	Fosaprepitant 150 mg
AUC_{0-t}, ng ∗ h/mL	97	43,729 (33)	44,130 (32)
AUC_{0-inf}, ng ∗ h/mL	95	45,460 (37)	46,163 (37)
C_{12h}, ng/mL	97	988 (28)	1022 (29)

AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of the last measurable plasma concentration; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{12h} = plasma concentration at 12 hours; PK = pharmacokinetics.

- 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{12h} were within bioequivalence bounds, consistent with comparable exposure (**Table 3**)

Table 3. Summary of Bioequivalence Analyses for Aprepitant (PK Population)

		90% CI	
PK Parameter	Point Estimate (Test/Reference) ∗ 100	Low	High
AUC_{0-t}, ng ∗ h/mL	98.99	96.675	101.354
AUC_{0-inf}, ng ∗ h/mL	98.23	95.517	101.026
C_{12h}, ng/mL	97.06	94.186	100.023

AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of the last measurable plasma concentration; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{12h} = plasma concentration at 12 hours; PK = pharmacokinetics.

Safety

- During the entire study period, fewer subjects had ≥ 1 TEAE with HTX-019 versus fosaprepitant (21% vs 28%) (**Table 4**)

Table 4. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

	HTX-019 130 mg N = 99	Fosaprepitant 150 mg N = 100	Overall N = 100
Subjects with ≥ 1 TEAE, n (%)	21 (21)	28 (28)	41 (41)
Subjects with related TEAE, n (%)	15 (15)	28 (28)	37 (37)
Subjects with TEAE leading to study discontinuation, n (%)	0	2 (2)*	2 (2)
Subjects with related TEAE leading to study discontinuation, n (%)	0	2 (2)*	2 (2)
Number of TEAEs	27	54	81
Number of related TEAEs	18	52	70
Number of TEAEs leading to study discontinuation	0	2	2
Number of related TEAEs leading to study discontinuation	0	2	2

*2 subjects discontinued from study drug because of moderate dyspnea.
TEAE = treatment-emergent adverse event.

- A negative binomial analysis of TEAEs found the estimated event rate per subject-day for HTX-019 was approximately half the rate observed for fosaprepitant (0.03 vs 0.06 TEAEs per subject-day, $P = 0.0274$)
- No severe TEAEs, serious TEAEs, or deaths occurred
- All TEAEs resolved by study end
- TEAEs in ≥ 3% of patients are shown in **Table 5**

Table 5. Treatment-Emergent Adverse Events (≥ 3% of Patients, Safety Population)

	HTX-019 130 mg N = 99	Fosaprepitant 150 mg N = 100	Overall N = 100
Headache, n (%)	5 (5)	8 (8)	12 (12)
Infusion-site pain, n (%)	1 (1)	9 (9)	10 (10)
Nausea, n (%)	1 (1)	5 (5)	6 (6)
Vessel puncture–site pain, n (%)	5 (5)	0	5 (5)
Dizziness, n (%)	1 (1)	4 (4)	4 (4)
Dysphnea, n (%)	1 (1)	3 (3)	4 (4)
Pain in extremity, n (%)	0	3 (3)	3 (3)
Somnolence, n (%)	1 (1)	2 (2)	3 (3)

- Within 1 hour of infusion start, fewer subjects receiving HTX-019 versus fosaprepitant had ≥ 1 TEAE (1% [infusion-site pain] vs 20% [including 8 subjects with infusion-site reactions]) (**Table 6**)
  - Most of the TEAEs occurred within the first 30 minutes

Table 6. Treatment-Emergent Adverse Events Within 1 Hour or 30 Minutes of Infusion Start (Safety Population)

	HTX-019 130 mg N = 99	Fosaprepitant 150 mg N = 100	Overall N = 100
Subjects with ≥ 1 TEAE, n (%)			
Within 1 h of infusion start	1 (1)	20 (20)	21 (21)
Within 30 min of infusion start	0	17 (17)	17 (17)
Number of TEAEs within 1 h of infusion start	1	32	33

TEAE = treatment-emergent adverse event.

- There were no clinically meaningful changes in clinical laboratory values, vital sign measurements, or 12-lead ECG results

CONCLUSIONS

- HTX-019 IV was shown to be bioequivalent to fosaprepitant IV
- HTX-019 IV was generally well tolerated, without the infusion-site reactions associated with fosaprepitant IV
- Fewer subjects receiving HTX-019 versus fosaprepitant reported TEAEs within 1 hour of infusion start
  - The majority occurred within the first 30 minutes
- HTX-019 IV may provide a safer alternative to fosaprepitant IV for patients with CINV

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Acknowledgments

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