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

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Presented by
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MASCC/ISOO
ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER

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Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patents	Stock Options	Ownership/ Equity Position	Employee	Other (Please Specify)
Heron Therapeutics	No	No	No	No	No	No	Yes	None

Chemotherapy-Induced Nausea and Vomiting (CINV)

- Consensus guideline–recommended treatment regimen for CINV following highly (HEC) and, frequently, for moderately emetogenic chemotherapy (MEC) comprises a 3-drug regimen:
  - 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist (RA)
  - dexamethasone
  - neurokinin 1 (NK-1) RA[1-4]
- Aprepitant, an NK-1 RA, is available only in an oral formulation (EMEND PO),[5] while fosaprepitant, an aprepitant prodrug,[6] was developed to provide an IV route of administration
  - Fosaprepitant IV is associated with hypersensitivity and infusion-site reactions, primarily attributed to its surfactant, polysorbate 80[7]
    - Hypersensitivity reactions include flushing, erythema, and dyspnea
    - Infusion-site reactions include pain, erythema, swelling, induration, and thrombophlebitis[8]

1. Basch et al. *J Clin Oncol.* 2011;29:4189-4198.
2. Hesketh et al. *J Clin Oncol.* 2015;34:381-386.
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4. NCCN Clinical Practice Guidelines in Oncology: Antiemesis—v1.2017.
5. EMEND oral [package insert]. Whitehouse Station, NJ: Merck & Co. Inc; 2015.
6. EMEND injection, for intravenous use [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2016.
7. Ten Tije et al. *Clin Pharmcokinet.* 2003;42:665-685.
8. Leal et al. *Support Care Cancer*. 2014;22:1313-1317.

Rationale and Objectives

- Rationale for HTX-019 development
  - HTX-019 is a polysorbate 80–free IV formulation of aprepitant
    - May provide a safer IV NK-1 RA option with a lower risk of hypersensitivity and infusion-site reactions
    - Improve patient adherence versus an oral regimen
- Study objectives
  - Primary: To determine the bioequivalence (BE) of HTX-019 to fosaprepitant IV in healthy subjects
  - Secondary: To evaluate safety and tolerability of HTX-019 and fosaprepitant IV in healthy subjects

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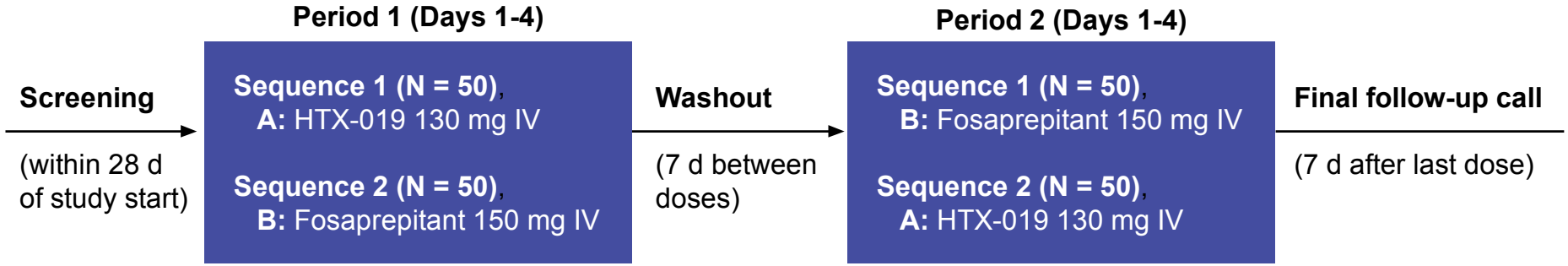
Study Design

- Phase 1, open-label, randomized, 2-way crossover BE and safety evaluation of HTX-019 and fosaprepitant, each agent administered as a single IV dose to healthy subjects



- Observation period: 72 hours for each treatment period

  Note: **Confinement lasted from 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.**

- Eligibility: Healthy men or women aged 18-55 years, ≥ 50 kg body weight (BMI 18-35 kg/m^2), and not pregnant or breastfeeding

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Methods

- Blood samples were collected before infusion start and 0.5-72 hours
  - All time points were analyzed for aprepitant
  - 0.5-1.5 hours were also analyzed for fosaprepitant
- Bioequivalence evaluation was based on aprepitant $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and postequilibrium plasma aprepitant concentrations (C_{12h})
- Bioequivalence was declared if 90% CI was within 80%-125%
- Safety evaluation included treatment-emergent adverse events (TEAEs) and serious AEs

$AUC_{0\text{-}t}$ = area under the time-concentration curve from zero to time t; $AUC_{0\text{-}inf}$ = area under the time-concentration curve from time zero extrapolated to infinity; C_{12h} = plasma concentration at 12 hours.

Results

- 100 subjects enrolled
  - 97 of 100 completed the study and were included in BE analysis
  - All subjects were included in the safety analysis
- Demographics and baseline characteristics were comparable between the 2 treatment sequences

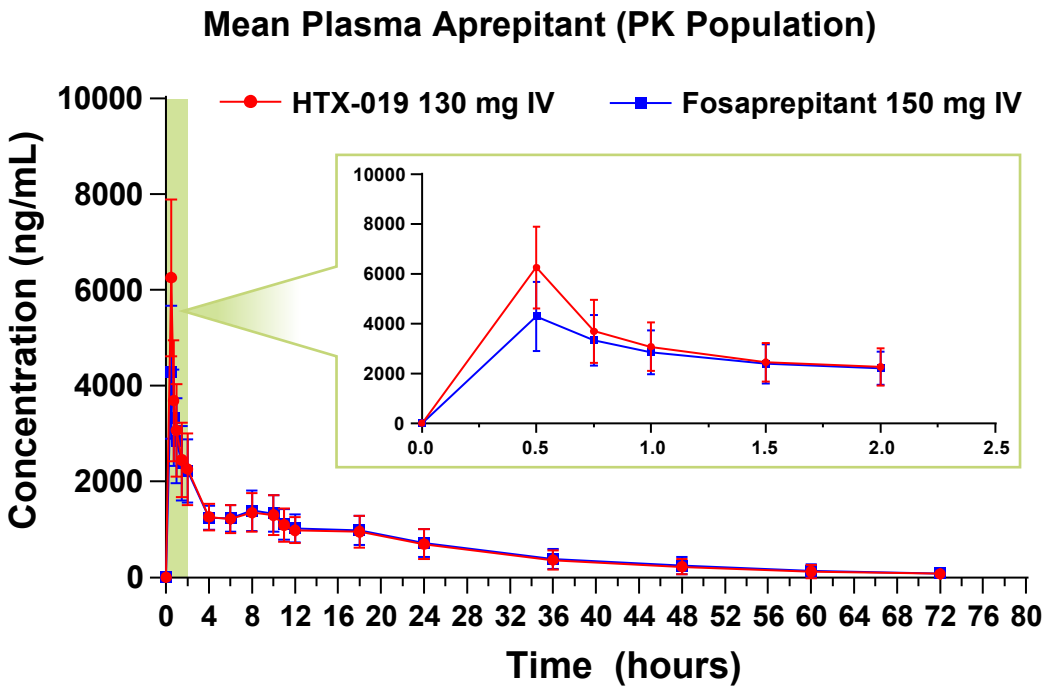
Demographics and Baseline Clinical Characteristics (Safety Population)

	Sequence I: AB N = 50	Sequence 2: BA N = 50	Overall N = 100
Age, mean (SD), y	38 (10)	33 (9)	35 (10)
Body mass index, mean (SD), kg/m^2	27 (3)	27 (4)	27 (4)
Sex, n (%) Female Male	 18 (36) 32 (64)	 18 (36) 32 (64)	 36 (36) 64 (64)
Race, white, n (%)	30 (60)	25 (50)	55 (55)

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

Results: Pharmacokinetics

- 90% CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{12h} were well within bioequivalence bounds, consistent with comparable exposure
- As expected, aprepitant mean C_{max} was slightly higher for HTX-019 than for fosaprepitant IV due to ongoing conversion of fosaprepitant to aprepitant
- Plasma aprepitant concentrations were essentially identical 15 minutes post-infusion through 72 hours



C_{max} = maximum concentration.

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Results: Safety

- During the entire study period, fewer subjects had ≥ 1 TEAE with HTX-019 versus fosaprepitant IV (21% vs 28%); fewer HTX-019 subjects had a related TEAE (15% vs 28%)
- There was a lower incidence of TEAEs within 1 hour (1% vs 20%) and within 30 minutes (0% vs 17%) with HTX-019 versus fosaprepitant IV
- Most of the TEAEs occurred within the first 30 minutes

Overall Summary of Treatment-Emergent Adverse Events (Safety Population)		
	HTX-019 130 mg N = 99	**Fosaprepitant 150 mg N = 100**
Subjects with ≥ 1 TEAE, n (%)	21 (21)	28 (28)
Subjects with related TEAE, n (%)	15 (15)	28 (28)
Subjects with TEAE leading to study discontinuation, n (%)	0	2 (2)*
Treatment-Emergent Adverse Events Within 1 Hour or 30 Minutes of Infusion Start (Safety Population)		
Subjects with ≥ 1 TEAE, n (%) Within 1 hour of infusion start Within 30 minutes of infusion start	 1 (1) 0	 20 (20) 17 (17)
Number of TEAEs within 1 hour of infusion start	1	32

*2 subjects discontinued study drug because of moderate dyspnea.

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Results: Safety

Treatment-Emergent Adverse Events in ≥ 3% patients in the Overall Study period (Safety Population)]		
	HTX-019 130 mg N = 99	**Fosaprepitant 150 mg N = 100**
Headache, n (%)	5 (5)	8 (8)
Infusion-site pain, n (%)	1 (1)	9 (9)
Nausea, n (%)	1 (1)	5 (5)
Vessel puncture site pain, n (%)	5 (5)	0
Dizziness, n (%)	1 (1)	4 (4)
Dyspnea, n (%)	1 (1)	3 (3)
Pain in extremity, n (%)	0	3 (3)
Somnolence, n (%)	1 (1)	2 (2)

- 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 IV
  - 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

Conclusions

- HTX-019 was bioequivalent to fosaprepitant IV
- HTX-019 was generally well tolerated, without the infusion-site reactions associated with fosaprepitant IV
  - The single case of dyspnea seen in the HTX-019 treatment group was not treatment-related and did not lead to discontinuation
  - 2 of 3 cases of dyspnea with fosaprepitant IV were treatment-related and led to study discontinuation
- Fewer subjects receiving HTX-019 versus fosaprepitant IV reported TEAEs within 1 hour of infusion start
  - The majority of TEAEs occurred within the first 30 minutes
- HTX-019 may provide a safer alternative to fosaprepitant IV for patients with CINV