Phase 1 Bioavailability Study of HTX-019 Intravenous Injection Compared with Aprepitant Oral Capsules

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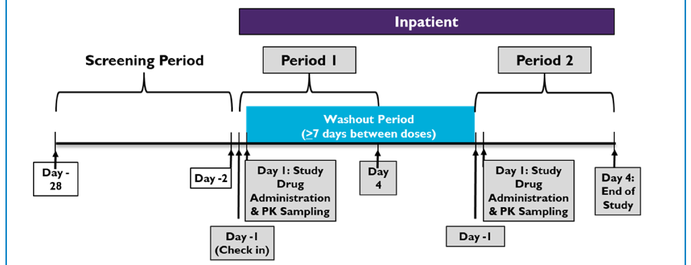
INTRODUCTION AND OBJECTIVES

- Postoperative nausea and vomiting (PONV) is a distressing complication occurring in 30% of postsurgical patients and up to 80% of high-risk patients[1].
- Substance P is a regulatory peptide that binds to neurokinin-1 (NK_1) receptors to trigger nausea and vomiting. NK_1 receptor antagonists are a well-established class of antiemetics with proven utility for PONV prophylaxis, as numerous studies demonstrate superior efficacy in preventing vomiting compared with other classes of antiemetics[2].
- Aprepitant is a selective high affinity NK_1 receptor antagonist. Oral (PO) aprepitant 40 mg is approved for the prevention of PONV[3].
- HTX-019 is an IV form of aprepitant recently FDA-approved for the prevention of PONV, which is formulated as an emulsion that can be administered as a 30-second injection to achieve rapid NK_1 receptor inhibition.
- The primary objective of this study was to evaluate the relative single-dose bioavailability of plasma aprepitant following HTX-019 32 mg administered as a 30-second IV injection compared with an aprepitant 40 mg capsule administered orally. Secondary objectives were to evaluate safety tolerability of HTX-019 32 mg administered as a 30 second IV injection and aprepitant 40 mg administered orally as a capsule.

METHODS

- This study was a Phase 1, open-label, randomized, 2-sequence, crossover, relative bioavailability study of IV HTX-019 and PO aprepitant in healthy adults. Study design is depicted in **Figure 1**.
- **Inclusion Criteria:** Age 18 to 55 years of age, > 50 kg, body mass index (BMI) between 18 and 35 kg/m^2, in good health as determined by a physician, females not pregnant, lactating, or planning to become pregnant during study.
- **Exclusion Criteria**: Contraindication or hypersensitivity to aprepitant, components of HTX-019, or other NK_1 antagonists; sustained blood pressure/heart rate outside of normal range or abnormal ECG deemed clinically significant; consumption of prescription medications (except vaccinations and hormonal contraceptives), herbal, or other nutraceuticals within 28 days, or over-the-counter medications and/or vitamins within 14 days; use of tobacco-containing products within 14 days, or alcohol, caffeine, fish liver oils, or grapefruit/grapefruit juice within 72 hours; positive test for drug(s) of abuse at initiation of study.
- **Treatment Assignments:** Patients were randomized to 1 of 2 treatment sequences (AB or BA) in a 1:1 fashion, with approximately 15 per treatment sequence. There was a minimum 7-day washout interval between the 2 single-dose administrations. Treatments were as follows:
  - Treatment A: HTX-019 32 mg administered as 30-second IV injection
  - Treatment B: Aprepitant 40 mg administered as oral capsule

Figure 1. Study Design



Abbreviations: AUC, area under the concentration-time curve; AUC_{inf}, AUC from Time 0 extrapolated to infinity; AUC_{last}, AUC from Time 0 to the time of the last quantifiable concentration; CL, total body clearance; CL/F, total body clearance corrected for bioavailability; C_{max}, maximum concentration; λ_z, apparent terminal elimination rate constant; $t_{½}$, apparent terminal half-life; T_{max}, time of occurrence of maximum concentration; V_z, total volume of distribution; V_z/F, total volume of distribution corrected for bioavailability.

METHODS, cont.

- **PK and Safety Endpoints:**
  - Primary PK: Area under the plasma concentration-time curve $(AUC)_{last}$ and AUC_{inf}
  - Secondary PK: C_{max}, T_{max}, λz, $t_{½}$, CL (HTX-019 only), CL/F (oral aprepitant only), V_z (HTX-019 only), V_z/F (oral aprepitant only)
  - Safety: Adverse events (AE)s, chemistry and hematology laboratory values, vital signs, and12-lead ECG
- Blood samples for plasma aprepitant concentrations were collected 15 minutes before dosing, at 5, 15, 30, and 60 minutes, and 2, 4, 6, 9, 12, 24, 36, 48, and 72 hours post-dose.
- Bioequivalence was declared if the 90% CIs for the geometric least squares mean ratios (GLSMRs) for HTX-019 and PO aprepitant AUC_{last} and AUC_{inf} were contained within the limits of 80 to 125%.
- Adverse events and vital signs were assessed throughout the study; clinical labs, ECGs, and physical examinations were collected/conducted at screening and Days 1 and 4 of each treatment period.

RESULTS

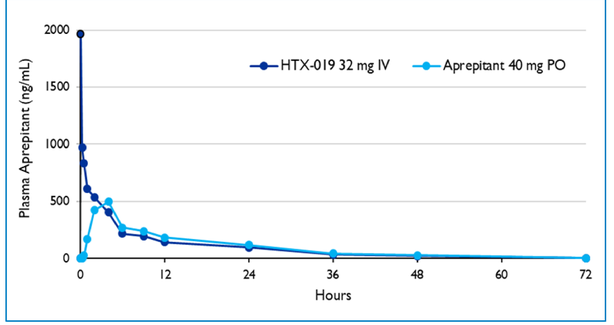
- 32 subjects were randomized and received study drug: 16 followed sequence AB and 16 followed sequence BA.
- Demographics and baseline characteristics were similar between treatment sequences. Mean (SD) age was 37.9 (9.59) years and there was equal number of men and women. Majority of patients were Black or African American (50.0%) or White (40.6%), and 81.3% were not Hispanic or Latino. Mean (SD) BMI was 27.3 (4.05) kg/m^2.
- Key PK parameters are displayed in **Table 1.** The mean C_{max} of aprepitant was 3.7-fold higher and the median T_{max} was substantially earlier and more consistent (5 minutes vs 4 hours) following HTX-019 32 mg IV compared with PO aprepitant 40 mg, which was expected given IV administration. Mean aprepitant plasma concentrations vs. time are in **Figure 2**.
- Bioequivalence was established based on AUC_{last} and AUC_{inf} (**Table 2**).

Table 1. Summary of Key Plasma Aprepitant Pharmacokinetic Parameters

Treatment	n[a]	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{½}$ (h)	CL[b] (L/h)	V_z[c] (L)
HTX-019 32 mg IV	31	0.084 (0.083-0.105)	2,029 (21.4)	6,748 (30.3)	7,225 (28.4)	11.52 (25.3)	4.790 (28.7)	76.65 (24.6)
Aprepitant 40 mg PO	32	4.00 (2.00-6.00)	542.3 (46.5)	6,635 (35.1)	7,152 (33.1)	11.66 (31.5)	6.113 (28.8)	98.92 (32.3)

Values are presented as mean (%CV) for all parameters except for T_{max}, for which median and range are presented. [a]1 patient had an atypical PK profile for HTX-019 which indicated infiltration into the subcutaneous tissues. This patient was excluded from the HTX-019 PK assessments. AUC_{inf}, $t_{½}$, clearance, and volume of distribution not reportable for 2 patients- adjusted coefficient of determination for linear regression (R^2_{adj}) did not meet acceptance criterion. [b]CL is reported for HTX-019 and CL/F is reported for oral aprepitant. [c]Vz is reported for HTX-019 and Vz/F is reported for oral aprepitant.

Figure 2. Mean Aprepitant Plasma Concentrations vs. Time



RESULTS, cont.

Table 2. Summary of Plasma Aprepitant AUC and C_{max} Bioequivalence Assessment

Treatment		n[a]	Geometric Least Squares Mean AUC_{inf} (h*ng/mL)	Geometric Least Squares Mean AUC_{last} (h*ng/mL)	Geometric Least Squares Mean C_{max} (ng/mL)
HTX-019 32 mg IV		31	6,841.89	6,456.08	1,976.92
Aprepitant 40 mg PO		32	6,846.29	6,294.78	497.58
Ratio (% of Ref)[b]			**99.94**	**102.56**	**397.31**
90% CI Limits	**Lower**		**93.95**	**95.17**	**355.70**
	Upper		**106.30**	**110.53**	**443.78**

[a]n=30 (HTX-019) and n=31 (oral aprepitant) for AUC_{inf}. AUC_{inf} not reportable for 2 patients- adjusted coefficient of determination for linear regression (R^2_{adj}) did not meet acceptance criterion. [b]Reference formulation was oral aprepitant capsule and test formulation was HTX-019 IV.

- The safety profile was similar for HTX-019 and PO aprepitant, and differences between treatments were considered attributable to the small sample sizes. Constipation was the most common possibly related event to treatment (**Table 3**). Analysis of AEs in the first hour after dosing indicated that the higher and earlier C_{max} with HTX-019 IV administration was not associated with AEs.
- All AEs were mild in severity and resolved by the end of study. There were no clinically meaningful changes in clinical laboratory values, vital sign measurements, or ECG parameters. There were no serious AEs or AEs that led to study drug discontinuation or study withdrawal.

Table 3. Summary of Adverse Events

Adverse events, n (%)	HTX-019 32 mg IV N=32	Aprepitant 40 mg PO N=32
Patients with ≥ 1 AE	9 (28.1)	4 (12.5)
Possibly related[a]	5 (15.6)	1 (3.1)
Patients with ≥ 1 Severe AE	0	0
Patients with ≥ 1 Serious AE	0	0
AEs leading to study withdrawal	0	0
Most common AEs		
Vessel puncture site pain[b]	3 (9.4)	3 (9.4)
Constipation	2 (6.3)	2 (6.3)

[a]5 events occurred following HTX 019 administration: constipation (2 events), fatigue (1 event), pain in extremity (1 event; considered likely due to inadvertent infiltration of HTX-019 into the subcutaneous tissues), and headache (1 event). One event (constipation) occurred following oral aprepitant administration. [b]5 of 6 were related to phlebotomy and 1 was related to IV line insertion.

DISCUSSION AND CONCLUSIONS

- HTX-019 32 mg IV achieved bioequivalence to aprepitant 40 mg PO based on AUC.
- The higher C_{max} and shorter T_{max} of HTX-019 compared to PO aprepitant was expected given its IV administration.
- Administration of HTX-019 32 mg IV resulted in rapid attainment of plasma concentrations associated with ≥ 97% brain NK_1 receptor occupancy (≥ 225 ng/mL) and maintenance of ≥ 90% brain NK_1 receptor occupancy (> 21 ng/mL) over 48 hours[4].
- Both treatments were well tolerated. The safety profile of HTX-019 was similar to that of PO aprepitant, and the higher and earlier C_{max} was not associated with an increase in AEs.
- These results support an application for approval of HTX-019 for PONV prevention, and offers the convenience of IV injection.

ACKNOWLEDGMENTS

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References: 1. Gan TJ. Anesth Analg 2020;131(2):411-48. 2. Jin Z. Drugs 2021;81:1171-79. 3. Aprepitant capsule full prescribing information. 4. Van Laere K. Clin Pharmacol Ther 2012;92(2):243-50.

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