Toxicology Assessment of High Concentration XeriJect® Trastuzumab Biosimilar Administered Subcutaneous in Cynomolgus Non-Human Primates

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BACKGROUND

The proprietary XeriJect® technology (Xeris Pharmaceuticals, Inc., Chicago, IL, USA) uses a novel viscoelastic suspension (VES) for delivery of high-concentration, low-volume subcutaneous (SC) injections of therapeutic antibodies.[1] Trastuzumab (TmAb) is a monoclonal antibody that selectively binds and inhibits human epidermal growth factor receptor 2 protein (HER2)[2] used for the treatment of certain types of breast, stomach, and esophageal cancer,[3] and is commercially available for both intravenous (IV) infusion and SC injection (Herceptin® IV and Herceptin Hylecta® SC, Genentech Inc., South San Francisco, CA, USA).[4] XeriJect TmAb biosimilar is a stable, high concentration (417 mg/mL) formulation of trastuzumab for SC administration, thus enabling lower injection volumes (**Figure 1**).

OBJECTIVE

This study evaluated the potential toxicity of XeriJect TmAb biosimilar SC compared to US-Herceptin IV infusion administered at 50 mg/kg/day weekly for up to five doses to cynomolgus non-human primates (NHP) in a GLP toxicology study.

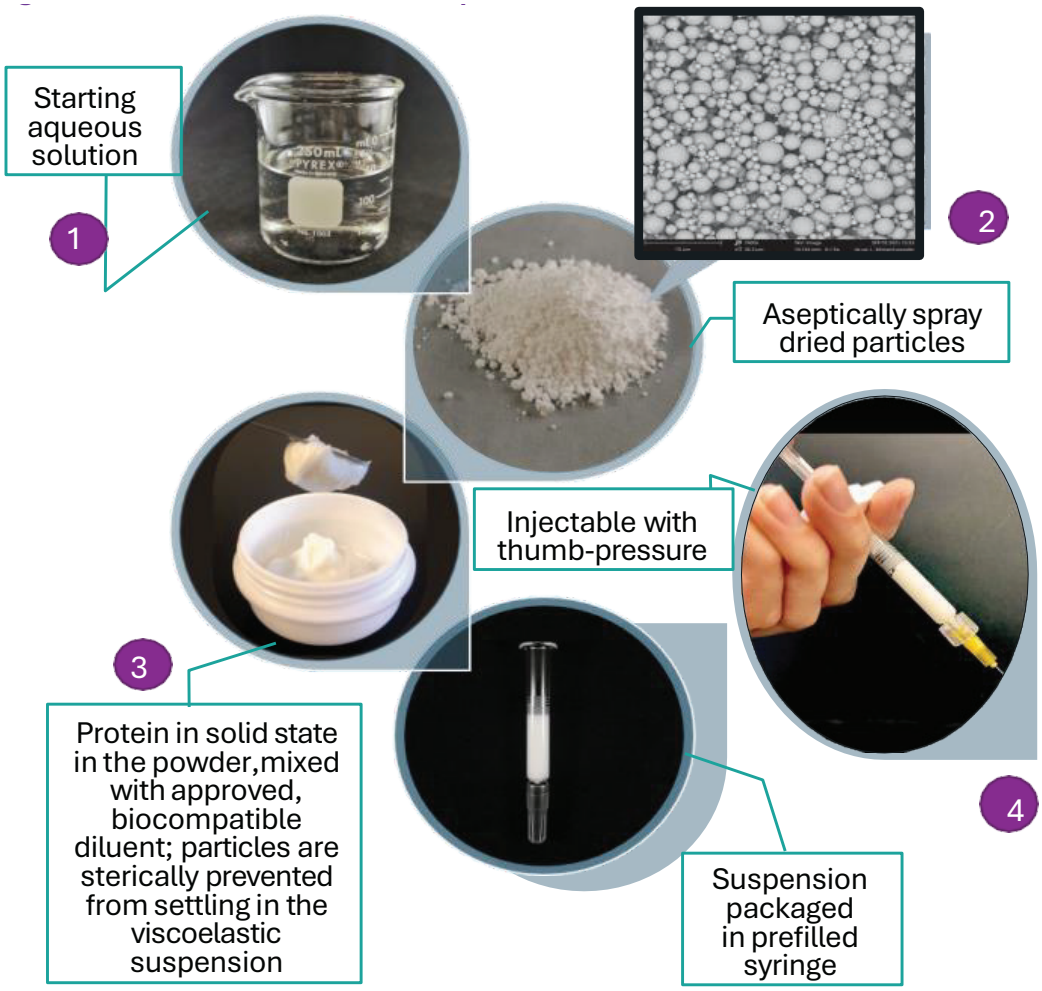
METHODS

- Cynomolgus monkeys were administered 5 weekly doses of XeriJect Vehicle (SC), XeriJect TmAb biosimilar (SC) or US-Herceptin (IV: 30 min infusion) in GLP toxicology study (**Table 1**). XeriJect TmAb biosimilar formulation excipients included L-Histidine, Glycine, Trehalose Dihydrate, Polysorbate 80 and Miglyol® 812.
- Parameters evaluated: Mortality, clinical signs, body weights, injection site observations, ophthalmology, ECG, clinical pathology, toxicokinetics (Day 1 and Day 22) and anti-drug antibodies (Day 30).
- Parameters evaluated at necropsy on Day 30: organ weights, and macroscopic and microscopic examinations.

Table 1. Experimental Design

Test Article (Route)	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Males	Females
XeriJect Vehicle (SC)	0	0.12	0	3	3
XeriJect TmAb (SC)	50	0.12	417	3	3
US-Herceptin (IV)	50	2.38	21	3	3

Figure 1. XeriJect TmAb Biosimilar Preparation Process



RESULTS

- **Toxicology**

  There were no XeriJect TmAb biosimilar-related mortality or clinical signs, or effects on body weights, ophthalmology, electrocardiographic examinations, clinical pathology parameters, organ weights, or macroscopic and microscopic examinations.

- **Injection Site Observations**

  Very slight or slight edema, but no erythema was noted in animals administered XeriJect Vehicle SC and XeriJect TmAb biosimilar SC. Sporadic instances of edema or erythema were noted in animals administered US-Herceptin IV.

  This study showed no injection site reactions related to SC administration of XeriJect TmAb biosimilar or IV administration of US-Herceptin.

- **Toxicokinetics**

  Systemic exposure to XeriJect TmAb biosimilar and US-Herceptin were independent of sex and increased similarly following repeated administration. XeriJect TmAb biosimilar bioavailability was ~74% on Days 1 and 22 (**Fig. 2, Table 2**).

- **Antidrug Antibodies (ADA)**

  No ADA were found on Day 30 after 5 weekly doses with XeriJect TmAb biosimilar or US-Herceptin.

Figure 2. Mean (± SD) Concentration vs. Time Curves for TmAb in Male and Female NHP Serum Following SC Administration of 50 mg/kg XeriJect TmAb biosimilar or 50 mg/kg IV Infusion of US-Herceptin

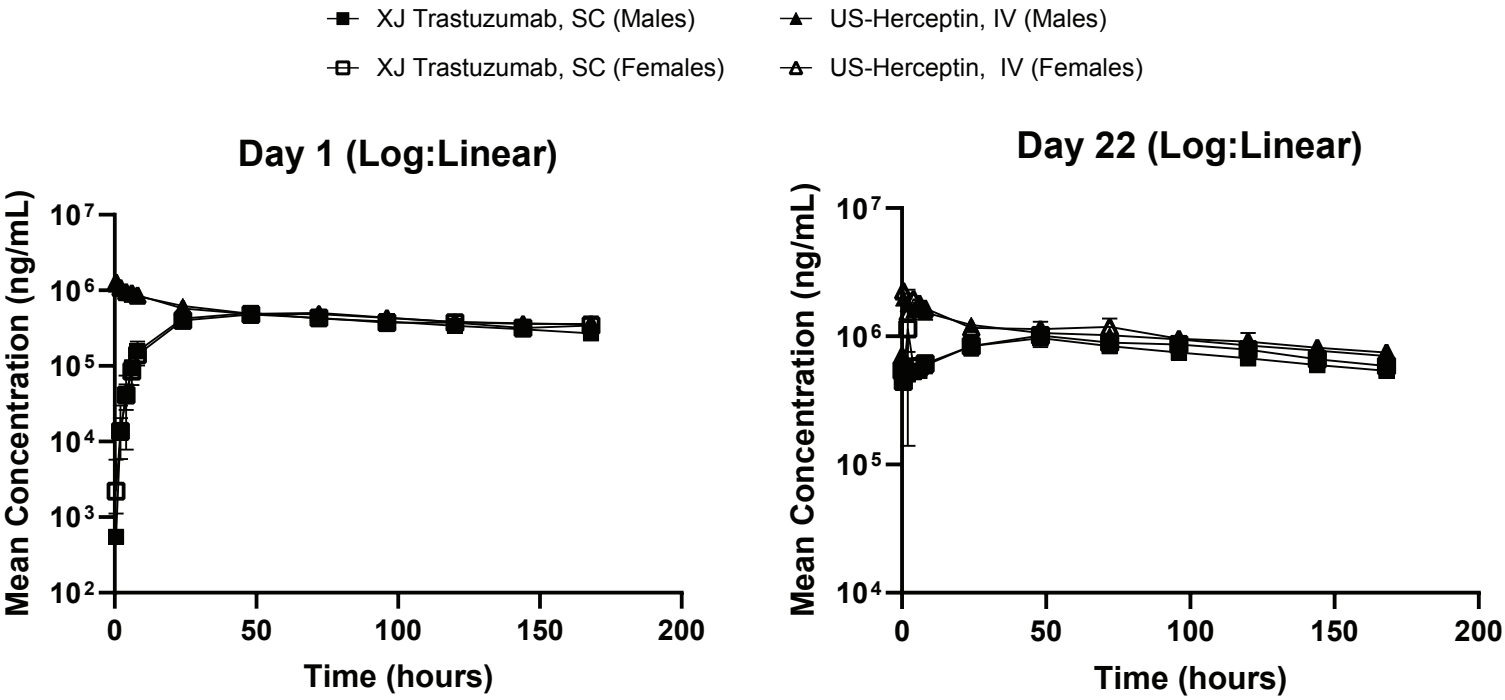


Table 2. Summary (Mean ± SD) Toxicokinetic Parameters of TmAb in Male and Female NHP Serum Following SC Administration of XeriJect TmAb biosimilar or IV Infusion of US-Herceptin

Dose (mg/kg/day)	Sex	Day	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}168hr}$ (hr*ng/mL)
XeriJect TmAb Biosimilar					
50	Combined (M/F)	1	492,000 ± 32,800	48	60,700,000 ± 5,730,000
50	Combined (M/F)	22	1,210,000 ± 552,000	48	130,000,000 ± 12,800,000
US-Herceptin					
50	Combined (M/F)	1	1,240,000 ± 54,700	0.5	82,500,000 ± 4,410,000
50	Combined (M/F)	22	2,120,000 ± 208,000	0.5	175,000,000 ± 13,100,000

CONCLUSION

XeriJect TmAb biosimilar is a stable, high-concentration, low-volume XeriJect Formulation that when delivered subcutaneous to cynomolgus NHP at 50 mg/kg/day weekly for five consecutive weeks was well tolerated compared to commercial US-Herceptin.

REFERENCES

1. Data on file. Xeris Pharmaceuticals, Inc.
2. Quartino AL, Hillenbach C, Li J, et al. Population pharmacokinetic and exposure-response analysis for trastuzumab administered using a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. *Cancer Chemother Pharmacol*. 2016;77(1):77-88.
3. Waller CF, Möbius J, Fuentes-Alburo A. Correction to: Intravenous and subcutaneous formulations of trastuzumab, and trastuzumab biosimilars: implications for clinical practice. *Br J Cancer*. 2024;131(3):611.
4. Herceptin® (trastuzumab) [package insert]. South San Francisco, CA: Genentech Inc.