PHARMACOKINETICS OF A NOVEL VISCOELASTIC SUSPENSION OF BEVACIZUMAB BIOSIMILAR FOR HIGH-CONCENTRATION, LOW-VOLUME SUBCUTANEOUS INJECTION

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Background:

- Xeris Pharmaceuticals, Inc. (Chicago, IL, USA) has developed the proprietary XeriJect™ formulation technology which uses a novel non-aqueous, viscoelastic suspension (VES) for delivery of low-volume, subcutaneous (SC) injections of highly concentrated therapeutic antibodies and proteins. These high-concentration therapeutics can be delivered subcutaneously at volumes smaller than required by other technologies, provides rapid absorption, and elimination kinetics similar to aqueous formulations.
- Bevacizumab (BmAb) is a humanized monoclonal antibody (mAb) that selectively binds to circulating Vascular Endothelial Growth Factor A (VEGF-A), thereby inhibiting the binding of VEGF-A to its receptors on the surface of endothelial cells and inhibiting angiogenesis.[1]
  - Used to treat metastatic colorectal cancer, non squamous cell lung cancer, metastatic breast cancer, ovarian cancer, cervical cancer, metastatic renal cell cancer, prostate cancer, and glioblastoma
  - Commercially available as Intravenous (IV) BmAb injection only (Avastin®, Genentech Inc., South San Francisco, CA, USA)[2]

Goal:

This study compared the pharmacokinetic profiles of two XeriJect™ (XJ) BmAb formulations, XJ-1 BmAb and XJ-2 BmAb (differing in their composition), administered subcutaneously, with commercial Avastin® administered IV or SC to Göttingen minipigs.

Methods[3]:

- 16 Göttingen minipigs (n=4 per treatment) were administered Avastin IV, Avastin SC, XJ-1 BmAb SC, and XJ-2 BmAb SC at a fixed dose of 100 mg (**Table 1**).
- The concentrations of XJ-1 BmAb and XJ-2 BmAb formulations were ~439 and 373 mg/mL, respectively, while commercial Avastin® was 26 mg/mL.

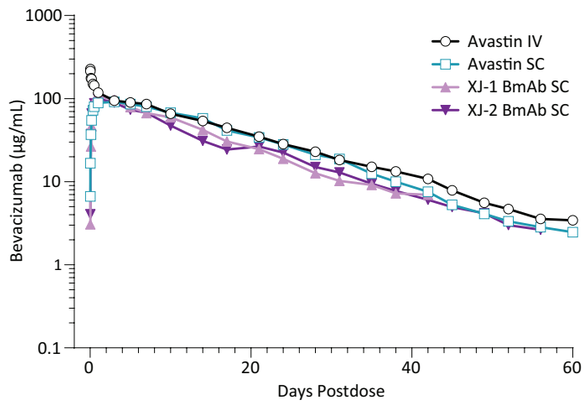
Table 1. Study Design

Treatment	Avastin IV	Avastin SC	XJ-1 BmAb SC	XJ-2 BmAb SC
Target Dose (mg)	100	100	100	100
Mean Dose (mg)	106	106	94	82
Mean Dose (mL)	4.1	4.1	0.21	0.22
Dose Concentration (mg/mL)	26	26	439	373

- Both XJ formulations consisted of spray dried powder (containing BmAb and stabilizing excipients) and comprised of spherical particles of mean size < 5 µm, blended with Miglyol® 812 N to produce the VES.
- Plasma was collected over 60 days.
- Non-compartmental analysis was conducted on plasma BmAb concentration-time levels using Phoenix 64 software version 8.2.0.4383 (Certara, USA).

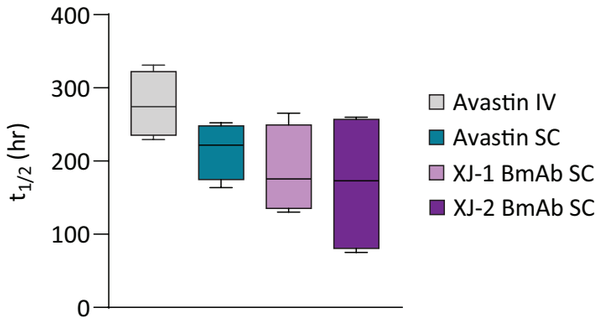
RESULTS

Mean Plasma Bevacizumab Concentration-Time Profile

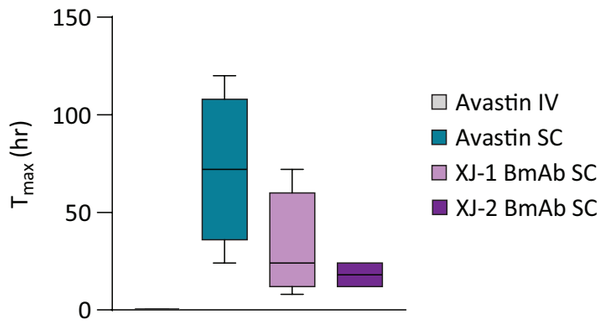


Semi-log scale of mean bevacizumab plasma concentration over time

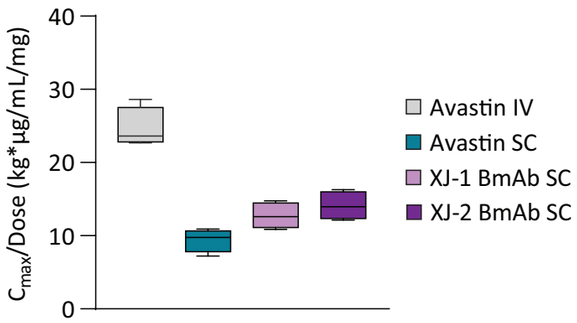
Elimination Half-Life



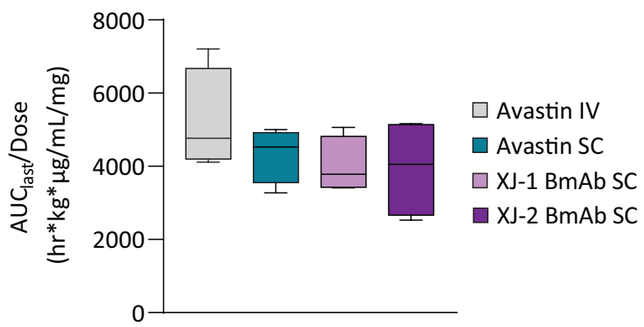
Time to Peak Drug Concentration



Maximum Plasma Concentration Relative to Dose



Exposure Relative to Dose



- XJ-1 BmAb SC and XJ-2 BmAb SC were rapidly absorbed with similar T_{max} and C_{max}/Dose (**Table 2**).
- Avastin SC median T_{max} was approximately 3 times longer with a mean C_{max}/Dose 26% and 33% lower than XJ-1 BmAb SC and XJ-2 BmAb SC.
- T_{max} was longer and C_{max}/Dose lower for all SC administered formulations compared to Avastin IV.
- All SC formulations showed similar elimination profiles and exposure as assessed by AUC_{last}/Dose.
- Bioavailability of XJ-1 BmAb SC and XJ-2 BmAb SC were both 77%, while Avastin SC was 83%.

Table 2. Pharmacokinetic Parameters of Plasma Bevacizumab after IV Administration of Avastin and SC Administration of Avastin and XeriJect Bevacizumab Formulations

Treatment	Avastin IV	Avastin SC	XJ-1 BmAb SC	XJ-2 BmAb SC
Median T_{max} (hr)	0.08	72	24	18
Mean [SD] C_{max}/Dose (kg*µg/mL/mg)	24.65 [2.73]	9.41 [1.56]	12.73 [1.74]	14.09 [1.91]
Mean [SD] AUC_{last}/Dose (hr*kg* µg/mL/mg	5214.69 [1387.45]	4333.92 [749.09]	4007.13 [764.68]	3953.04 [1354.34]
Mean [SD] elimination half-life (hr)	277.33 [45.0]	214.81 [38.58]	186.73 [60.33]	170.16 [97.25]

CONCLUSIONS:

We have demonstrated for the first time that administration of bevacizumab formulated via XeriJect™ into a stable, non-aqueous, high-concentration formulation for SC administration can produce rapid absorption and pharmacokinetics similar to commercially available Avastin® administered IV and SC in a preclinical pharmacokinetic model.

References:

1. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev.* 2020;86:102017.
2. Avastin® (bevacizumab) [package insert]. South San Francisco, CA: Genentech Inc.; 2022.
3. Data on file. Xeris Pharmaceuticals, Inc.

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