Safety, Tolerability, and Pharmacokinetics of BJT-778, a Monoclonal Antibody for Treatment of Chronic Hepatitis B and Chronic Hepatitis D, Following Single Ascending Doses in Healthy Volunteers

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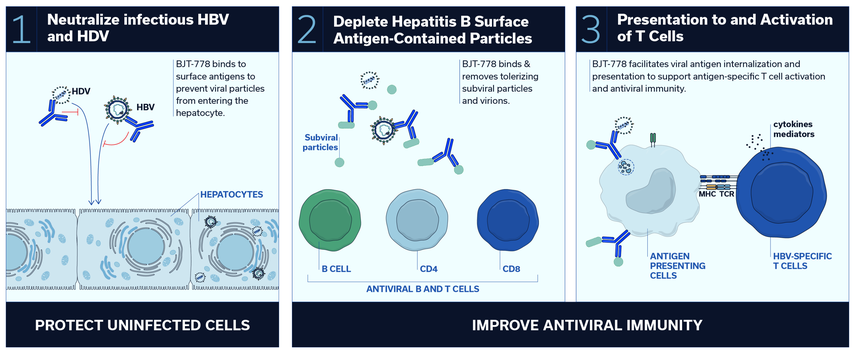
Background

- Close to 300 million people worldwide have chronic hepatitis B infection (CHB)[1].
- An estimated 12 million of those with CHB also are chronically coinfected with hepatitis D (CHD)[2].
- There is an unmet need for curative treatments for CHB and for effective well-tolerated treatments for CHD that reduce disease progression.
- BJT-778 is a fully human monoclonal antibody that targets HBsAg and is currently under evaluation for the treatment of CHB as well as CHD.
- BJT-778 has received PRIME designation and a positive opinion for orphan drug designation by the European Medicines Agency for the treatment of HDV.

BJT-778 has Multiple Modes of Action



Objectives of BJT-778-001 Part A

To evaluate the safety, tolerability and pharmacokinetics of BJT-778 in healthy subjects.

Methods

- Cohort A of Part 1 of the 2-part study is a Phase 1a/1b double-blind, randomized, placebo-controlled single-ascending-dose in healthy male and female volunteers between the ages of 18 to 55.
- 8 subjects per dosing cohort were randomized in a 3:1 ratio to receive a subcutaneous dose of BJT-778 or placebo (normal saline) subcutaneously. Doses chosen were 75, 300 and 900 mg.

75 mg → **300 mg** → **900 mg**

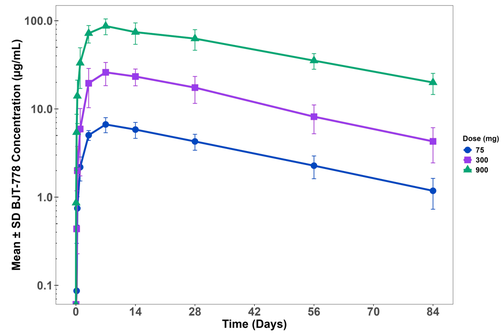
- Pharmacokinetic samples were collected at multiple timepoints on Study Day 1, and then on Study Days 2, 4, 8, 15, 29, 57, and 85.
- Serum concentrations of BJT-778 were determined by a validated noncompetitive immunoassay employing electrochemiluminescence detection on the Meso Scale Discovery platform, with an LLOQ of 0.25 µg/mL.
- PK parameters were estimated using noncompartmental analysis method of linear up/log down and summarized using descriptive statistics in Phoenix® WinNonlin®, v8.4 (Certara L.P., Princeton, New Jersey, USA).
- The study is ongoing, and the data remain blinded.

Results

Demographics of Enrolled Subjects

	75 mg | N=8	300 mg | N=8	900 mg | N=8
Median age, years (range)	34 (23-43)	27 (21-46)	34 (21-45)
Sex, n (%)			
Men	4 (50%)	4 (50%)	3 (37.5%)
Women	4 (50%)	4 (50%)	5 (62.5%)
Race, n (%)			
White	2 (25%)	5 (62.5%)	3 (37.5%)
Asian	3 (37.5%)	1 (12.5%)	2 (25%)
Pacific Islander	2 (37.5%)	1 (12.5%)	1 (12.5%)
American Indian or Alaska native	0	0	1 (12.5%)
White/Pacific Islander mix	1 (12.5%)	0	1 (12.5%)
Not Reported	0	1 (12.5%)	0
Hispanic/Latino	0	0	2 (25%)
Median BMI, kg/m² (range)	26.2 (22.4-34.2)	26.2 (19.1-31.3)	21.9 (20.8-26.3)

PK results – Healthy Volunteer Only



Preliminary BJT-778 Pharmacokinetic Parameters After a Single Subcutaneous Dose in Healthy Volunteers

	75 mg | N=6	300 mg | N=6	900 mg | N=5*
T_{max} (day)	7.00 (7.00-14.0)	7.00 (7.00-14.0)	7.00 (7.00-7.00)
C_{max} (µg/mL)	6.63 (19.3%)	25.1 (33.7%)	85.6 (20.9%)
C_{max}/D (µg/mL/mg)	0.0884 (19.3%)	0.0835 (33.7%)	0.0951 (20.9%)
T_{last} (day)	84.0 (84.0-84.0)	84.0 (84.0-84.0)	84.0 (84.0-84.0)
C_{last} (µg/mL)	1.12 (35.9%)	3.88 (56.3%)	19.4 (26.5%)
AUC_{last} (day*µg/mL)	276 (20.1%)	1030 (39.1%)	3920 (21.6%)
AUC_{inf} (day*µg/mL)	325 (24%)	1190† (42.1%)	4970‡ (23.1%)
AUC_{inf}/D (day*µg/mL)	4.34 (24%)	3.97† (42.1%)	5.52‡ (23.1%)
$t_{1/2}$ (day)	29.6 (12.6%)	27.2 (16.3%)	35.9 (22%)
CL/F (mL/day)	230 (24%)	252 (42.1%)	181 (23.1%)
V/F (L)	9.86 (16.7%)	9.88 (35%)	9.39 (28.1%)

Note: All parameters are displayed as geometric mean (geometric CV%) except for T_{max} and T_{last}, which are presented as median (minimum, maximum). *1 subject was withdrawn at the discretion of the PI from study on Day 4 due to aggressive behavior with the staff and thus removed from summary statistics as data was insufficient for estimation of parameters to provide any meaningful analysis. †1 subject had AUC_{inf}% extrapolated >20% (21.6%), requiring more data for accurate estimation. ‡4 subjects had AUC_{inf} % extrapolated > 20% (20.7-27.6%), requiring more data for accurate estimation. AUC: area under the plasma concentration-time curve; AUC_{inf}: AUC from time 0 to infinity; AUC_{last}: AUC to last measurable concentration; C_{last}: last measurable concentration; CL/F, apparent clearance; C_{max}: maximum concentration; D: dose; T_{last}: time of last measurable concentration; T_{max}: time to reach C_{max}, $t_{1/2}$, half-life; V/F, apparent volume of distribution.

- Cmax of BJT-778 was achieved at 7 days post dose with geometric mean elimination t1/2 of approximately 27 to 36 days across all dose levels.
- The Cmax and AUCinf increased proportionally between 75 mg to 900 mg.
- In vitro, the half maximal effective concentration (EC50) values for neutralization of HBV and HDV infections were 0.09 and 0.01 nM, respectively, and plasma concentrations consistently exceeded the EC50 for all doses levels over the 84-day sampling period.

Adverse Events (Blinded)

	75 mg/placebo N=8	300 mg/placebo N=8	900 mg/placebo N=8
Subjects with any AE	6	8	7
Subjects with any AE at least possibly related to treatment	1[a]	1[a]	2[a]
Subjects with AEs leading to discontinuation	0	0	0
Subjects with Grade 2, 3, or 4 AEs	0	0	0
Subjects with SAEs	0	0	0

[a] 3 subjects with injection site bruising including 1 also with injection site swelling; 1 subject with fatigue possibly related to treatment

- BJT-778 was well tolerated.
- All AEs were mild (Grade 1) and most were unrelated to treatment.

Conclusions

- Single SC doses of BJT-778 up to 900 mg was **safe and well tolerated** in healthy volunteers.
- **Dose-proportional increases** in BJT-778 C_{max} and AUC_{inf} were observed across all dose levels.
- BJT-778 demonstrated a **long half-life** of 27-36 days.
- All dose levels achieved and **sustained high plasma concentrations** above the EC50 for the entire sample period of 84 days.
- The **favorable safety profile and PK properties** of subcutaneous administration of BJT-778 support continued development for the treatment of CHB as well as CHD.

References

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2. Stockdale AJ, et al. Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, Hutin Y, Geretti AM. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol. 2020 Sep;73(3):523-532.

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