Single Dose Safety, Tolerability and Pharmacokinetics of AB-423 in Healthy Volunteers from the ongoing Single and Multiple Ascending Dose Study AB-423-001

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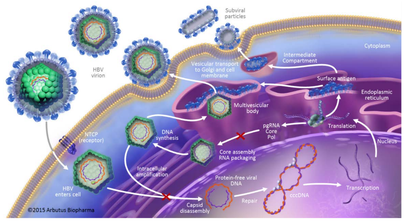
Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

- Hepatitis B virus (HBV) causes the world's most common serious liver infection; up to 350 million people globally may be chronically infected with HBV[1,2]
- Proper assembly of the HBV nucleocapsid is essential for viral genome relaxed circular DNA (rcDNA) synthesis, infectious virion production and maintenance of a nuclear covalently closed circular DNA (cccDNA) pool
- The capsid assembly process thus represents a bona fide antiviral target and constitutes a novel mechanism that is distinct from the nucleos(t)ide analogues currently available for clinical use[3]
- AB-423 is a potent, orally administered, highly selective HBV capsid inhibitor being developed to treat chronic Hepatitis B virus infection (CHB)
- In cell culture, AB-423 inhibited HBV pgRNA encapsidation and cccDNA formation (Fig 1)

Figure 1: Hepatitis B Virus life cycle depicting the sites of AB-423 inhibition



AB-423 blocks HBV pgRNA encapsidation and inhibits the formation of cccDNA (presumably via inhibition of the capsid uncoating step). This mechanism of action can potentially result in inhibition of viral assembly and associated decreases in HBV genome replication, cccDNA replenishment and hepatic reinfection cycles in patients with CHB.

- AB-423 is primarily metabolized by CYP3A4 into 3 major (ARB-168554, ARB-168711 and ARB-168735) and 4 minor metabolites
- The major metabolites retain activity against HBV (Table 1)

Table 1: Antiviral activity of AB-423 and major metabolites of AB-423 in HepDE19 cell culture model

Compound	AB-423	ARB-168554	ARB-168711	ARB-168735
Mean (SD) EC50 (μM)[a]	0.262 (0.127)	1.676 (0.538)	0.900 (0.367)	0.702 (0.192)

[a] values based on N≥4 independent determinations

OBJECTIVES

Objectives of Single Dose Cohorts of AB-423-001:

- Primary: to evaluate the safety, tolerability and pharmacokinetics (PK) of AB-423 following single oral administration to healthy subjects
- Secondary: to characterize the PK of selected metabolites of AB-423 in healthy subjects

MATERIALS AND METHODS

- AB-423-001 is an ongoing randomized, double blind, placebo controlled single and multiple ascending dose study in healthy volunteers (Fig 2)

Figure 2: AB-423-001 single ascending dose panels (n=8/group – 6 active: 2 placebo)

12.5 mg → 37.5 mg → 100 mg → 200 mg → 400 mg → 800 mg

Key Design Elements:

- Population: Eligible study participants were healthy adult subjects aged 18-55 years and BMI 18-32 kg/m². Healthy subjects were defined as individuals free from clinically significant illness or disease as determined by their medical history, physical examination, vital signs and clinical laboratory test results
- Each sequential dose panel used two sentinel subjects given AB-423 or placebo (1:1)
- Doses of AB-423 were administered after an overnight fast
- Subjects remained in-house for 72 hours after study drug administration prior to furlough and a follow up visit on Day 14
- Approximately 7-10 days after dosing, subject safety and PK were evaluated to enable escalation to the next sequential dose

Study Assessments:

- **Safety:** Subjects were monitored for treatment emergent AEs and vital sign measurements, physical examinations, electrocardiograms (ECGs) and clinical laboratory tests were collected throughout the study
- **PK:** Blood samples were collected pre-dose and over 72 hours post-dose for quantification of AB-423 and its major metabolites (ARB-168554, ARB-168711 and ARB-168735) in plasma via validated LC/MS/MS methods
- Noncompartmental PK parameters were derived and descriptive statistics were prepared by dose panel using Phoenix WinNonlin (version 7.0; Pharsight, Certara USA, Princeton, NJ)

RESULTS

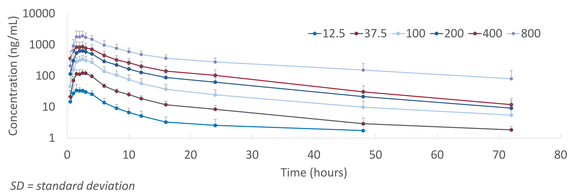
Demography

Forty-seven of 48 subjects were male with a mean age of 38.0 years and mean BMI of 25.9 kg/m². The majority were white (93.8%) and non-Hispanic or Latino (85.4%).

Pharmacokinetics

AB-423 Pharmacokinetics

Figure 3: Mean (±SD) plasma concentration of AB-423 versus time by dose panel



SD = standard deviation

Table 2: Summary statistics of plasma PK parameters for AB-423

Plasma PK Parameter	AB-423 Dose Panel (mg) 12.5 N=6	37.5 N=6	100 N=6	200 N=6	400 N=6	800 N=6
Cmax (ng/mL) Geometric Mean (CV%)	40.8 (33)	135.8 (22)	376.4 (22)	643.6 (40)	881.1 (38)	2030 (30)
Tmax (hours) Median (min, max)	2.5 (0.5, 4.0)	2.25 (1.5, 3.0)	2.5 (1.0, 4.0)	2.5 (1.5, 4.0)	2.0 (1.0, 6.0)	2.0 (1.5, 6.0)
AUC(0-∞) (ng*h/mL) Geometric Mean (CV%)	244.2 (41)	984.7 (23)	2850 (34)	5667 (41)	8878 (37)	26032 (37)
T-HALF (hours) Mean (SD)	8.1 (5.2)	15.3 (3.3)	18.4 (5.3)	16.1 (4.1)	15.1 (2.4)	26.2 (12.1)

Cmax = maximum concentration; Tmax = time to maximum concentration; AUC(0-∞) = area under the plasma concentration time curve from time of dosing extrapolated to infinite time; T-HALF = terminal elimination half-life; SD = standard deviation; CV = coefficient of variation

- AB-423 appears to be absorbed quickly with no apparent lag time and Tmax of approximately 2-2.5 hours post-dose
- Concentrations of AB-423 appear to have a bi-phasic decline and T-HALF of approximately 15 to 18 hours; T-HALF at 800 mg was higher but more variable
  - There were low/unquantifiable concentrations of AB-423 after 24 hours in the 12.5 mg dose panel in some subjects leading to an apparent underestimation of T-HALF and AUC(0-∞)
- Variability in AB-423 PK appears to be low to moderate with CV for Cmax and AUC(0-∞) generally 30-40% across dose panels
- Using a power model to assess dose proportionality, Cmax of AB-423 was slightly less than dose proportional (β = 0.9066) and AUC(0-∞) of AB-423 was slightly more than dose proportional (β= 1.0756) across the entire dosing range (Fig 4 & Fig 5)

Figure 4: Power model AB-423 Cmax

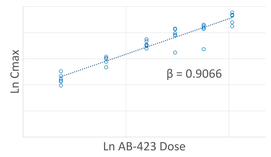
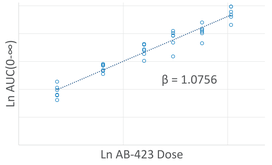


Figure 5: Power model AB-423 AUC(0-∞)



Pharmacokinetics of Major Metabolites of AB-423

A representative plot of mean concentration versus time data for AB-423 with its major metabolites is presented in Figure 6

Figure 6: Mean concentration of AB-423 and major metabolites following 100 mg dose of AB-423

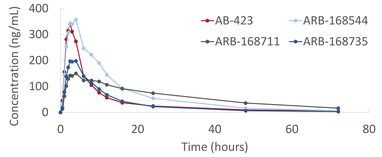


Table 3: Summary statistics of plasma PK parameters for ARB-168554

Plasma PK Parameter	AB-423 Dose Panel (mg) 12.5 N=6	37.5 N=6	100 N=6	200 N=6	400 N=6	800 N=6
Cmax (ng/mL) Geometric Mean (CV%)	43.0 (26)	115.0 (18)	379.5 (11)	704.3 (51)	1310 (41)	2483 (33)
AUC(0-∞) (ng*h/mL) Geometric Mean (CV%)	464.2 (28)	1672 (38)	4858 (22)	9460 (41)	17078 (34)	40456 (46)
Metabolic Ratio Geometric Mean (CV%)	2.22 (38)	1.99 (22)	1.99 (17)	1.95 (50)	2.25 (23)	1.82 (54)

Table 4: Summary statistics of plasma PK parameters for ARB-168711

Plasma PK Parameter	AB-423 Dose Panel (mg) 12.5 N=6	37.5 N=6	100 N=6	200 N=6	400 N=6	800 N=6
Cmax (ng/mL) Geometric Mean (CV%)	24.5 (70)	43.1 (56)	117.7 (90)	269.7 (51)	433.5 (46)	1104 (69)
AUC(0-∞) (ng*h/mL) Geometric Mean (CV%)	247.0 (120)	400.3 (94)	1470 (140)	3436 (66)	5476 (66)	22636 (85)
Metabolic Ratio Geometric Mean (CV%)	0.97 (104)	0.39 (95)	0.50 (125)	0.58 (106)	0.59 (89)	0.83 (105)

Table 5: Summary statistics of plasma PK parameters for ARB-168735

Plasma PK Parameter	AB-423 Dose Panel (mg) 12.5 N=6	37.5 N=6	100 N=6	200 N=6	400 N=6	800 N=6
Cmax (ng/mL) Geometric Mean (CV%)	34.5 (19)	72.9 (10)	217.0 (13)	353.6 (38)	503.0 (37)	906.2 (16)
AUC(0-∞) (ng*h/mL) Geometric Mean (CV%)	286.2 (19)	775.6 (18)	2302 (23)	4532 (24)	6808 (20)	16468 (28)
Metabolic Ratio Geometric Mean (CV%)	1.12 (21)	0.76 (9)	0.78 (20)	0.77 (38)	0.74 (21)	0.61 (11)

Cmax = maximum concentration; Tmax = time to maximum concentration; AUC(0-∞) = area under the plasma concentration time curve from time of dosing extrapolated to infinite time; CV = coefficient of variation; Metabolic Ratio = AUC(0-∞) of metabolite divided by AUC(0-∞) of AB-423 corrected for molecular weight

- Rapid appearance of major metabolites in plasma suggests metabolism of AB-423 via intestinal or first pass hepatic CYP3A4
- Median Tmax for all metabolites was generally 2.5-3.0 hours post-dose (not shown)
- Mean T-HALF for metabolites was approximately 9 to 19 hours (not shown)
- Variability in PK led to greater inconsistency in metabolic ratio for ARB-168711; across doses the geometric mean metabolic ratio was 0.62

Safety

Note: Study AB-423-001 remains blinded due to ongoing multiple dose panels

Among the SAD dose panels:

- There were no serious AEs (SAEs), deaths or discontinuations
- Treatment-emergent AEs (considered study drug related per Investigator) occurred in 10 out of 48 subjects (20.8%) dosed with either AB-423 or placebo (Table 6)
  - All AEs were mild except one Grade 2 elevated lipase (asymptomatic) and resolved prior to study discharge
  - The Grade 2 elevated lipase (102 U/L) occurred on study Day 4 of the 800 mg Dose Panel without any accompanying clinical symptoms and normalized prior to study discharge. This subject also had a pre-study Grade 2 lipase elevation (191 U/L). There were no other clinically significant laboratory abnormalities
- There were no dose-related trends in AEs observed
- There were no clinically significant changes in vital signs, ECGs or physical exams

Table 6: Treatment emergent adverse events considered related to study treatment observed in ≥2 subjects

Reported Term	12.5 mg (n=8)	37.5 mg (n=8)	100 mg (n=8)	200 mg (n=8)	400 mg (n=8)	800 mg (n=8)	Total (n=48)
Number of subjects with an event	0	0	2 (25%)	4 (50%)	1 (12.5%)	3 (37.5%)	10 (20.8%)
Headache	0	0	0	1	1	1	3 (6.25%)
Soft/loose stool	0	0	1	1	0	1	3 (6.25%)
Nausea	0	0	0	1	0	1	2 (4.2%)
Heartburn	0	0	1	0	1	0	2 (4.2%)
Back pain/dorso-lumbar pain	0	0	0	1	0	1	2 (4.2%)
Dizziness/lightheaded						2	2 (4.2%)

- Other related AEs that occurred only once included: itchiness of hand/elbow, eye pain, ear redness, abdominal pain, bloated stomach, respiratory discomfort and fast heartbeat

CONCLUSIONS

- AB-423 Cmax was slightly less than dose proportional and AUC(0-∞) was slightly more than dose proportional from 12.5 to 800 mg single doses
- ARB-168554 was the most abundant metabolite formed from AB-423 (Metabolic Ratio ~2.0)
- Typical metabolic ratios for ARB-168735 and ARB-168711 were both <1.0 with greater variability for ARB-168711
- PK data suggest that major metabolites may contribute to antiviral activity in the clinic
- AB-423 has been generally well-tolerated at single doses up to 800 mg
  - No SAEs, deaths or discontinuations
  - No clinically significant changes in vital signs, ECGs or physical exams
  - All AEs were mild or moderate and resolved prior to study discharge
  - No dose-related trends in AEs observed
- A favorable safety and PK profile support further evaluation of multiple-dose administration of AB-423

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