HIF-2α Inhibitor AB521 Modulates Erythropoietin Levels in Healthy Volunteers Following a Single Oral Dose


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OVERVIEW

HIF-2α is a transcription factor that is an oncogenic driver in cancer that can promote tumor growth in ccRCC cases.

AB521 is a novel, potent HIF-2α inhibitor that can prevent HIF-2α-dependent gene transcription and block tumor progression in preclinical models.

Here we present the preliminary safety, pharmacokinetic (PK), and PD data from the first-in-human study of AB521 in healthy volunteers.

METHODS: Clinical Study Design

AB-521 is a first-in-human, placebo-controlled, randomized, phase 1 study with single- and multiple-ascending dose study design with drug-drug interaction, to evaluate the safety, tolerability, and PK profile of AB521.

The study is ongoing and has enrolled a total of 40 subjects to date (randomized 3:1 AB521:placebo).

RESULTS: Disposition and Characteristics

AB521 PK assay: The analytes (AB521) and internal standard (AB521-d6) were extracted from plasma using solid-phase extraction (SPE) and analyzed by UPLC-MS/MS with a lower limit of quantification of 100 ng/mL.

RESULTS: Bioanalytical Assays

METHODS: PK Simulation of AB521 Steady-State PK Profiles after QD Dosing

We would like to thank Drs. Assem el Baghdady, Lawrence Lu, Mohammad Ghasemi, Rebecca Ray for their contributions to the conduct of ARC-14 study.

RESULTS: Pharmacokinetic Profiles

Potential HIF-2α inhibition by AB521 was observed in healthy volunteers with reductions in serum erythropoietin (EPO), a proximal PD marker for HIF-2α inhibition.

Dose-dependent reductions in serum EPO were observed following a single dose at 10 mg, with a maximum mean reduction of baseline up to 80%

Following multiple dosing at 15 mg (QD for 7 days), sustained EPO reduction was observed throughout the dosing period.

EPO levels recovered rapidly after the end of AB521 dosing.

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2. Dose-dependent reductions in serum EPO were observed following a single dose at 10 mg, with a maximum mean reduction of baseline up to 80%

3. Following multiple dosing at 15 mg (QD for 7 days), sustained EPO reduction was observed throughout the dosing period.

4. EPO levels recovered rapidly after the end of AB521 dosing.

5. Mean ± SD serum EPO reduction-time profiles after a single or multiple oral dose(s) of AB521.

CONCLUSIONS

RESULTS: Safety and Tolerability

Preliminary data from the first-in-human study suggested that AB521 is well tolerated with minimal adverse events observed after a single dose (up to 100 mg) and multiple doses (highest dose tested to date of 15 mg QD).

The study is ongoing and higher dose levels are being evaluated.

Summary of study drug-related treatment-emergent adverse events

CONCLUSIONS

AB521 showed favorable PK profiles with:

• Multiple-ascending dose supporting once daily dosing;

• Exposure increasing with dose in the dose range tested (3-100 mg);

• Lack-of-three-way interaction, potentially minimizing Cmax-related toxicity while providing sustained PD effect.

Preliminary population PK modeling suggested that AB521 doses 30 mg QD would yield greater than the Cmax for HIF-2α inhibition in the majority of volunteers.

Potential Populations of AB521 Steady-State PK Profiles after QD Dosing

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Population PK Simulations of AB521 Steady-State PK Profiles after QD Dosing

METHODS: Pharmacokinetic Profiles

RESULTS: PKPD Summary

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3 mg

6 mg

100 mg

AB521

Placebo

RESULTS: Subject Disposition and Characteristics

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The study is ongoing and higher dose levels are being evaluated.

Overall summary of treatment-emergent adverse events

RESULTS: Pharmacodynamic Profiles

After multiple oral dosing (15 mg), the PK Profile is time-invariant and mean AUC showed no significant Cmax-related toxicity while providing sustained PD effect.

Preliminary AB521 PK parameters after single or multiple oral doses in healthy volunteers

Hydroxylation

Proteosome inhibition

HIF-2α inactivation

HIF-1α inactivation

Angiogenesis inactivation

Cmax

Time to peak Cmax (h)

AUC

Half-life (h)

τ

AUC0-τ

Population PK Simulations of AB521 Steady-State PK Profiles after QD Dosing

METHODS: Bioanalytical Assays

RESULTS: Pharmacokinetic Profiles

Following single (3 to 100 mg) or multiple (15 mg QD) dosing of AB521, median time to reach peak concentration (Cmax) was 3.5-4.3 hours, followed by multiphasic decline to plasma concentrations.

Mean apparent terminal half-life was 18-24 hours, supporting once daily dosing.

AUC increased in an approximately dose-proportional manner between 3 and 30 mg, and slightly less than dose proportional manner between 30 and 150 mg.

After multiple oral dosing (15 mg), the PK Profile is time-invariant and mean AUC increased least-squares fit (LSQ), which can help minimize population Cmax-related toxicity while providing sustained PD effect.

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