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Abstract 58

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

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OVERVIEW

- Hypoxia-inducible factor (HIF)-2α is a transcription factor that is an oncogenic driver in clear cell renal cell carcinoma (ccRCC).
- The post-translational regulation of the HIF-2α protein is oxygen-dependent and, in hypoxic or pseudohypoxic conditions, results in the stabilization of HIF-2α and downstream transcription of tumor-inducing genes.
- HIF-2α inhibition has been shown clinically[1] to mitigate tumor growth in ccRCC cases with mutation or dysregulation of the von Hippel-Lindau tumor suppressor gene.
- AB521 is a novel, potent, and selective allosteric small molecule inhibitor that can prevent HIF-2α-dependent gene transcription and block tumor progression in preclinical models.[2]
- Erythropoietin (EPO) is hormone produced in the kidney under the control of HIF-2α and as such, EPO is a relevant peripheral pharmacodynamic (PD) biomarker to assess HIF-2α inhibition.
- Here we present the preliminary safety, pharmacokinetic (PK), and PD data from the first-in-human single- and multiple-ascending dose study for AB521 in healthy volunteers.

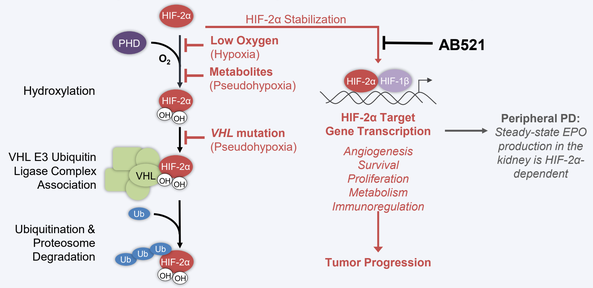
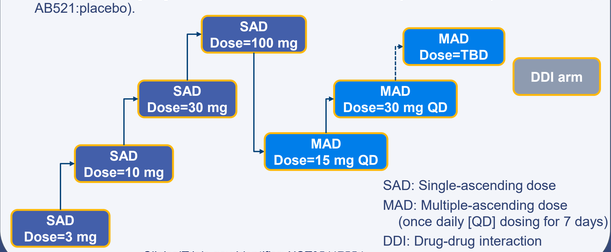


Figure 1. HIF-2α drives physiological changes to adapt to low oxygen that are hijacked by the tumor. HIF-2α is a transcription factor comprised of two proteins: a stably-expressed β subunit (HIF-1β/ARNT) and an oxygen-sensitive α subunit (**HIF-2α**). In hypoxic or pseudohypoxic conditions, HIF-2α is stabilized and drives transcriptional programs that promote tumor progression.

METHODS: Clinical Study Design

- ARC-14 is a first-in-human, participant and investigator-blinded, randomized, placebo-controlled, single- and multiple-ascending dose study with drug-drug interaction, to investigate the safety, tolerability, and PK profile of AB521, in healthy volunteers.
- The study is ongoing and has enrolled a total of 40 subjects to date (randomized 3:1, AB521:placebo).



ClinicalTrials.gov Identifier: NCT05117554

METHODS: Bioanalytical Assays

- AB521 PK assay: The analyte (AB521) and internal standard (AB521-d6) were extracted from plasma with acetonitrile. Concentrations of AB521 were determined by LC-MS/MS with a lower limit of quantification of 1.00 ng/mL.
- Erythropoietin (EPO) PD assay: Serum samples collected before and after dosing of AB521 or placebo were analyzed for EPO concentration using the Immulite 2000 (Siemens) analyzer with a limit of detection of 1.0 mIU/mL.

RESULTS: Subject Disposition and Characteristics

Characteristic	SAD Cohorts (Single dose)					MAD Cohort (QD dose x 7)	
		AB521					AB521
	Placebo N = 8	3 mg N = 6	10 mg N = 6	30 mg N = 6	100 mg N = 6	Placebo N = 2	15 mg N = 7*
Age, years							
Median (range)	22 (18-37)	23 (18-55)	22 (20-52)	28 (18–45)	22 (18-26)	24 (22-25)	24 (20-38)
Sex, n							
Male	0	0	0	0	0	0	0
Female	8	6	6	6	6	2	7
Fertility Status, n							
Childbearing Potential	8	5	5	6	6	2	7
Non-childbearing Potential	0	1	1	0	0	0	0
Race, n							
White	8	3	6	6	6	2	7
Asian	0	3	0	0	0	0	0
Black	0	0	0	0	0	0	0
Ethnicity, n							
Not Hispanic or Latino	8	6	6	6	6	2	7
Hispanic or Latino	0	0	0	0	0	0	0
BMI, kg/m^2							
Median (range)	23 (20- 29)	23 (19-25)	23 (19-24)	23 (20- 27)	24 (22-27)	23 (20-27)	23 (20-28)

SAD: single ascending dose; MAD: multiple ascending dose; QD: once daily; BMI: body mass index; Min: minimum; Max: maximum; SD: standard deviation; *one participant withdrew their consent for personal reasons 1 hour post first dose and was replaced per protocol. Site location: Netherlands.

RESULTS: Safety and Tolerability

- Preliminary data from the first-in-human study suggested that AB521 is well tolerated with minimal adverse events observed after 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.

Overall summary of treatment-emergent adverse events

Participants with	SAD Cohorts (single dose)					MAD Cohort (QD dose x 7)	
		AB521					AB521
	Placebo N = 8 n (%)	3 mg N = 6 n (%)	10 mg N = 6 n (%)	30 mg N = 6 n (%)	100 mg N = 6 n (%)	Placebo N = 2 n (%)	15 mg N = 7* n (%)
Any AE	11 (88)	15 (83)	20 (100)	13 (83)	19 (83)	6 (100)	22 (100)
Treatment-related AE	1 (13)	2 (33)	3 (50)	0	4 (67)	2 (50)	4 (29)
Grade 1 AE	11 (88)	15 (83)	20 (100)	13 (83)	19 (83)	6 (100)	22 (100)
Treatment-related Grade 1 AE	1 (13)	2 (33)	3 (50)	0	4 (67)	2 (50)	4 (29)
Death	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0
Discontinuation due to AE	0	0	0	0	0	0	0

N: total number of participants; n=number of individual events; %=percentage of participants with at least one event; SAD: single-ascending dose; MAD: multiple-ascending dose; QD: once daily; AE: adverse event; SAE: serious adverse event; *One participant withdrew their consent for personal reasons 1 hour post first dose and was replaced per protocol.

Summary of study drug-related treatment-emergent adverse events

MedDRA preferred term	SAD Cohorts (single dose)					MAD Cohort (QD dose x 7)	
		AB521					AB521
	Placebo N = 8 n (%)	3 mg N = 6 n (%)	10 mg N = 6 n (%)	30 mg N = 6 n (%)	100 mg N = 6 n (%)	Placebo N = 2 n (%)	15 mg N = 6 n (%)
Somnolence*	1 (13)	1 (17)	0	0	1 (17)	0	0
Headache	0	1 (17)	3 (50)	0	1 (17)	1 (50)	0
Heaviness in limbs	0	0	0	0	1 (17)	0	0
Abdominal bloating	0	0	0	0	1 (17)	0	0
Abdominal pain**	0	0	0	0	0	1 (50)	1 (17)
Fatigue	0	0	0	0	0	0	1 (17)
Vertigo	0	0	0	0	0	0	1 (17)
Emesis***	0	0	0	0	0	0	1 (17)

N: total number of participants; n=number of individual events; %=percentage of participants with stated event; MedDRA: Medical Dictionary for Regulatory Activities; *Somnolence includes intermittent somnolence; **Abdominal pain includes intermittent abdominal pain; ***Emesis includes intermittent emesis.

RESULTS: Pharmacokinetic Profiles

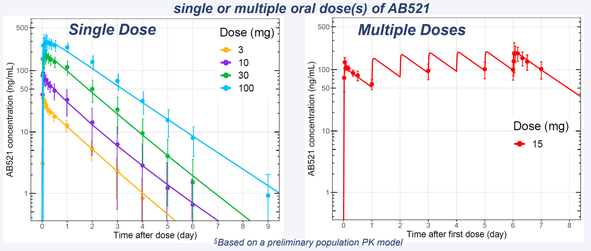
- Following single (3 to 100 mg) or multiple (15 mg QD) oral dosing of AB521, median time to reach peak concentration (T_{max}) was 1 to 3.5 hours, followed by multiphasic decline in plasma concentrations.
- Mean apparent terminal half-life is 18-24 hours, supporting once daily dosing.
- AUC increased in an approximately dose-proportional manner between 3 and 30 mg, and slightly less than dose proportional manner between 30 and 100 mg.
- After multiple oral dosing (15 mg), the PK Profile is time-invariant and mean AUC accumulation ratio is 1.7. The peak-to-trough ratio is low (~2), which can help minimize potential C_{max}-related toxicity while providing sustained PD effect.

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

Dose (mg)	Dosing Frequency	Day 1					Day 7			
		C_{max} (ng/mL)	T_{max} (h)	AUC_t (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	C_{trough} (ng/mL)	AUC_τ (h*ng/mL)
3	Single	39.5 (24%)	1.0 (1.0-2.0)	-	822 (25%)	20.1 (20%)	-	-	-	-
10	Single	95.0 (29%)	1.0 (0.5-6.0)	-	2180 (44%)	17.9 (42%)	-	-	-	-
15	QD	132 (19%)	1.0 (1.0-1.0)	1950 (13%)	-	-	203 (32%)	1.5 (1.0-4.0)	102 (31%)	3360 (29%)
30	Single	190 (26%)	3.0 (1.0-6.0)	-	6650 (28%)	18.2 (20%)	-	-	-	-
100	Single	338 (28%)	3.5 (0.5-6.0)	-	15200 (23%)	23.8 (15%)	-	-	-	-

Note: Mean (%CV) for C_{max}, AUC_{inf} and $t_{1/2}$. Median (range) for T_{max}. **Abbreviations**: *AUC_{inf} = area under plasma concentration-time curve from time zero extrapolated to infinity; AUC_τ= AUC from one dosing interval (τ; 24 h); C_{max} = maximum plasma concentration; C_{trough} = trough concentration; T_{max} = time to maximum plasma concentration; $t_{1/2}$ apparent terminal elimination half-life.*

Observed (mean ± SD) vs model-predicted§ AB521 concentration-time profiles after a single or multiple oral dose(s) of AB521

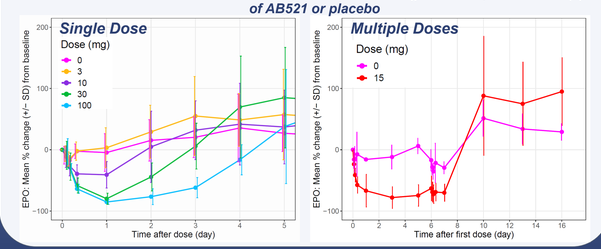


§Based on a preliminary population PK model

RESULTS: Pharmacodynamic Profiles

- Potent 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 to 100 mg, with mean maximum reduction from baseline up to 85%.
- 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.

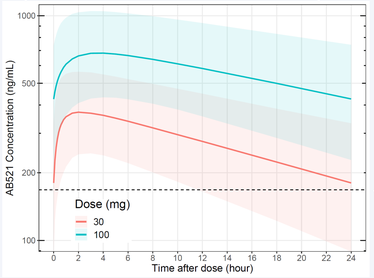
Mean ± SD serum EPO reduction-time profiles after a single or multiple oral dose(s) of AB521 or placebo



RESULTS: PK/PD Summary

- AB521 showed favorable PK profiles with:
  - Half-life ~18-24 hours supporting once daily dosing;
  - Exposure increasing with dose in the dose range tested (3-100 mg);
  - Low peak-to-trough ratio (~2), potentially minimizing C_{max}-related toxicity while providing sustained PD effect.
- Potent HIF-2α inhibition by AB521 was demonstrated by dose-dependent reductions (up to ~85%) in serum EPO following a single dose at 10-100 mg and sustained EPO reduction after multiple dosing at 15 mg QD.
- Preliminary population PK modeling suggested that AB521 doses ≥30 mg QD would yield C_{trough} above the IC_{90} for HIF-2α inhibition (from *in vitro* assay§) in the majority of subjects.

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



Solid line: Population median.
Shaded areas: 5th to 95th quantile of interindividual variability in predicted AB521 concentrations

IC_{90} for HIF-2α inhibition from in vitro assay§ (168 ng/mL or 383 nM)

§HIF-2α 786-O luciferase reporter assay in 100% serum

CONCLUSIONS

- 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.
- AB521 showed favorable PK profiles with half-life of 18-24 hours supporting once daily dosing. The exposure increases with dose in the dose range tested (3-100 mg). The low peak-to-trough ratio (~2) is expected to minimize potential C_{max}-related toxicity while providing sustained PD effect.
- Potent HIF-2α inhibition was demonstrated by dose-dependent reductions in serum EPO observed following a single dose (10-100 mg) and multiple doses (15 mg), with mean maximum reduction up to approximately 85%. The EPO reduction was transient followed by rapid recovery after the end of AB521 dosing.
- In this first-in-human study, AB521 demonstrated PK/PD properties that are consistent with a potential best-in-class HIF-2α inhibitor profile.
- The results from current study support the initiation of a Phase 1 study of AB521 in patients with ccRCC and other solid tumors at a pharmacologically active dose (ClinicalTrials.gov Identifier: NCT05536141).

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