Clinical Pharmacokinetic/Pharmacodynamic (PK/PD) Relationship Confirms Best-in-class Potential of Casdatifan (AB521), a Small Molecule Inhibitor of HIF-2α Being Developed in Renal Cancer

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BACKGROUND

- Hypoxia-inducible factor (HIF)-2α is a transcription factor that is an oncogenic driver in clear cell renal cell carcinoma (ccRCC)
- HIF-2α inhibition has been shown clinically to mitigate tumor growth in ccRCC cases that have a high frequency of von Hippel-Lindau tumor suppressor gene mutation or dysregulation
- AB521, an orally bioavailable small-molecule inhibitor of HIF-2α, potently inhibits transcription of HIF-2α-dependent genes in cell lines and preclinical species

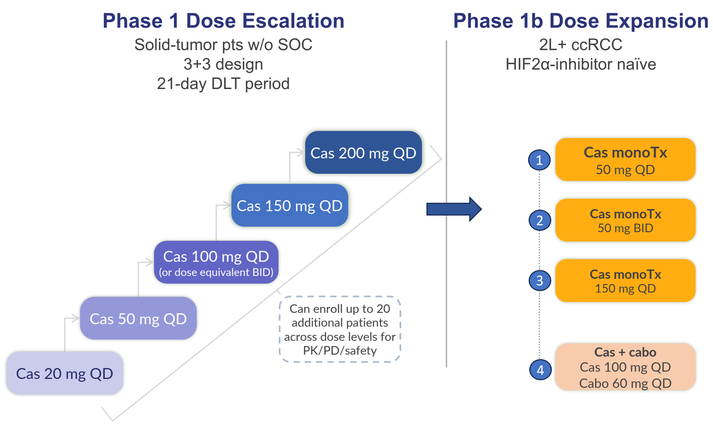
OBJECTIVES

- To develop an understanding of the relationship between casdatifan dose, PK, and changes in erythropoietin (EPO), a PD biomarker for peripheral (non-tumor) HIF-2α inhibition, and hemoglobin (Hb)
- To use this information to guide dose selection in future clinical trials

METHODS: CLINICAL STUDY DESIGN

- Casdatifan plasma concentrations, serum EPO concentration, and hemoglobin data were obtained from
  - 79 healthy participants in two Phase 1 studies, ARC-14 (NCT05117554) and ARC-28 (NCT05999513), and from
  - 71 patients with clear cell renal cell carcinoma (ccRCC) and other solid tumors in an ongoing Phase 1 study, ARC-20 (NCT05536141)
- A population PK/PD model was developed to correlate casdatifan dose, time course of PK and changes in EPO and Hb

ARC-20: Clinical Study Design



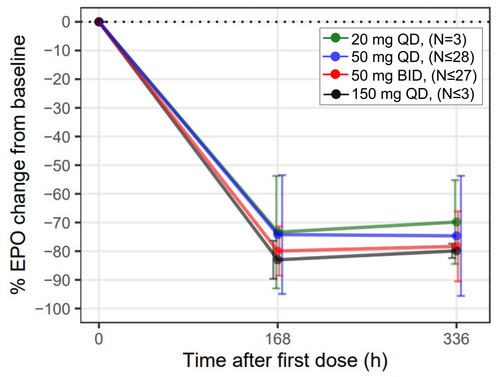
ARC-20 (NCT05536141) is a Phase 1, multicenter, open-label, first-in-patient study that is currently open for enrollment in the United States and South Korea. BID: twice daily; Cabo: cabozantinib; Cas: casdatifan; DLT: dose-limiting toxicity; SOC: standard of care; QD: once-daily; Tx: therapy.

CONCLUSION

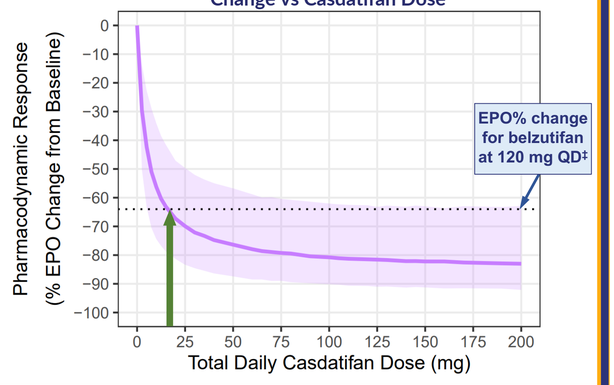
- Casdatifan showed potential best-in-class PK/PD profile with dose-proportional exposure over the tested range (3 to 150 mg)
- Casdatifan 20 mg QD provided a similar level of EPO suppression in ccRCC patients as belzutifan 120 mg QD (benchmark peripheral PD)
- Casdatifan dose of 100 mg had 5X higher exposure than 20 mg
- Overall, the casdatifan dose of 100 mg, selected for further development, allows exploration of the full therapeutic potential of HIF-2α inhibition

RESULTS: PK/PD RELATIONSHIP

ARC-20 Change in EPO (Mean ± SD) vs Time in Patients with ccRCC and other Solid Tumors



PK/PD model-derived Relationship of EPO Change vs Casdatifan Dose



Solid lines: Median of simulated concentrations
Shaded areas: 5th and 95th percentiles of simulated concentrations
‡ Source : Belzutifan NDA - FDA review document

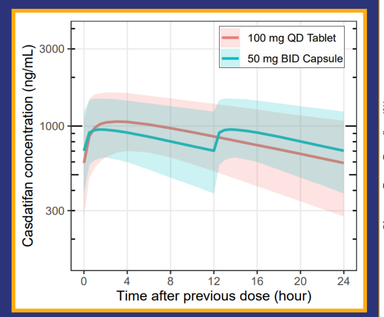
Casdatifan Exposure Increases ~5X from 20 to 100 mg Daily Dose

Casdatifan Daily Dose	20 mg		100 mg
Steady-state Daily AUC (h*µg/mL)	4.08	5X →	20.3

AUC values estimated from the population PK model

- A 20 mg daily dose of casdatifan is predicted to provide similar PD effect as 120 mg belzutifan
- The selected casdatifan dose of 100 mg daily provides ~5X higher exposure than 20 mg daily casdatifan, resulting ~5X higher exposure than that associated with the benchmark peripheral PD
- Based on simulations, the steady-state plasma casdatifan exposure as well as the PD effect are similar between the 50 mg twice daily (BID) capsule and 100 mg QD tablet, indicating that these two dosing regimens are interchangeable

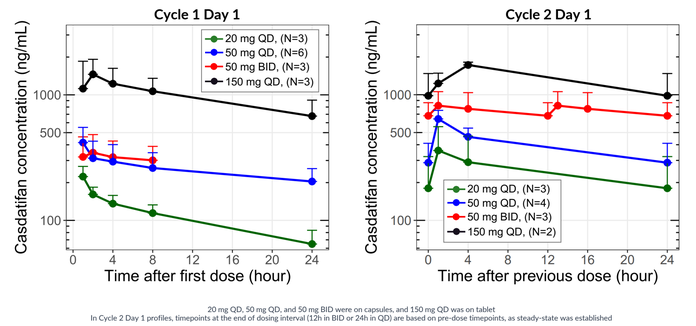
PopPK Simulations of Casdatifan Steady-State PK Profile after 50 mg BID Capsule and 100 mg QD Tablet



RESULTS: PHARMACOKINETIC PROFILES

- Following single or multiple oral dosing of casdatifan, median time to reach peak concentration (T_{max}) at Day 1 was 1.0 to 4.0 hours and at steady-state was 1.0 to 2.0 hours, followed by biphasic decline in plasma concentrations
- Mean terminal half-life was ~ 18 to 24 hours, supporting QD dosing
- Casdatifan showed dose-proportional exposure increase over the dose range tested (3 to 150 mg)
- After multiple daily dosing, casdatifan reached steady state around Day 4 with ~2.0-fold accumulation, indicating lack of time-dependent PK
- Casdatifan PK was similar between healthy participants and patients with cancer

Mean (+SD) Casdatifan Plasma Concentration vs Time Profiles Following Single or Multiple Oral Dose(s) of Casdatifan in Patients with Cancer (Study ARC-20)



20 mg QD, 50 mg QD, and 50 mg BID were on capsules, and 150 mg QD was on tablet
In Cycle 2 Day 1 profiles, timepoints at the end of dosing interval (12h in BID or 24h in QD) are based on pre-dose timepoints, as steady-state was established

RESULTS: PHARMACODYNAMIC PROFILES

- Potent HIF-2α inhibition was demonstrated by dose-dependent reductions in serum EPO:
  - In healthy participants (Study ARC-14), this was observed following a single dose (10-100 mg) and multiple doses (15, 30, or 50 mg QD for 7 days), with mean maximum reduction from baseline up to 85%
  - All patients in the Study ARC-20 cohorts (20 mg to 150 mg QD) showed significant decline in EPO levels relative to predose levels, with mean maximum reduction from baseline up to around 80%

Mean Serum EPO Reduction-Time Profiles Following Single or Multiple Oral Dose(s) of Casdatifan or Placebo in Healthy Participants (Study ARC-14)