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ORIGINAL ARTICLE

Pharmacokinetics, pharmacodynamics and safety of casdatifan, a novel hypoxia-inducible factor-2α inhibitor, in healthy participants

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Aims: Casdatifan is an orally bioavailable small-molecule hypoxia-inducible factor-2α (HIF-2α) inhibitor currently in development for treating patients with clear cell renal cell carcinomas. The aim of this study was to characterize the pharmacokinetics (PK), pharmacodynamics and safety of casdatifan in healthy participants.

Methods: This first-in-human study (NCT05117554) investigating casdatifan in 70 healthy participants consisted of 3 parts: a double-blind, randomized, placebo-controlled single ascending dose (3–100 mg) part; a multiple ascending dose (15–50 mg once daily) part; and an open-label, fixed sequence, 2-period, drug–drug interaction part to evaluate the effect of multiple doses of casdatifan on the single-dose PK of midazolam.

Results: In healthy participants, casdatifan plasma exposure increased dose proportionally over a single dose of 3–100 mg and multiple daily doses of 15–50 mg. The mean half-life of casdatifan was approximately 24 h, and PK parameters did not change over time. Dose- and concentration-dependent reduction, ranging from 41 to 85%, in erythropoietin (a pharmacodynamic biomarker for peripheral, nontumour, HIF-2α inhibition) was observed after single and multiple doses, consistent with HIF-2α pathway inhibition. Results from the midazolam drug–drug interaction part indicated that casdatifan was a weak CYP3A4 inducer at the tested dose. Urine PK data showed that approximately 30% of the overall casdatifan clearance appears to be via renal clearance.

Conclusions: Casdatifan, after single and multiple dosing in healthy participants, was safe and tolerable. Linear PK was associated with a mean maximum erythropoietin reduction of 85% following a single dose and multiple doses of casdatifan, demonstrating a promising exposure–biological activity profile.

The authors confirm that the Principal Investigator of this study (NCT05117554) was Maria Velinova, MD, PhD, of ICON Early Clinical & Bioanalytical Solutions, Groningen, The Netherlands, and that she had direct clinical responsibility for the study participants.

KEYWORDS
erythropoietin, hypoxia-inducible factor-2α inhibitor, oncology, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Hypoxia-inducible factor-2α (HIF-2α) is a transcription factor that modulates the cellular responses to hypoxia. The posttranslational regulation of the HIF-2α protein is mediated by **von Hippel–Lindau tumour suppressor protein (pVHL)** and oxygen dependent and, in hypoxic or pseudohypoxic conditions, stabilizes HIF-2α and downstream transcription of tumour-inducing genes.[1–4] Up to 80% of patients with clear cell renal cell carcinoma (ccRCC) have a defective pVHL, which results in accumulation of HIF-2α subunits.[5–8] In these patients, HIF-2α promotes tumorigenesis and disease progression.[1,9]

To date, **belzutifan** is the only approved therapy available in the USA to inhibit the tumorigenic effect of HIF-2α in patients with a defective pVHL pathway and advanced renal cell carcinoma (RCC).[10] Several other tumour types may also benefit from HIF-2α inhibitor therapies, including pheochromocytoma and paraganglioma, glioblastoma multiforme and pancreatic adenocarcinoma due to significantly higher levels of expression of HIF-2α.[1] Belzutifan clinical activity may be limited by saturable absorption with the approved dose of 120 mg yielding maximal exposure in humans.[11,12] **Erythropoietin** (EPO) is a well-characterized and specific pharmacodynamic biomarker of HIF-2α inhibition that has been used to measure the on-target activity of belzutifan and other HIF-2α inhibitors.[12,13]

Casdatifan, previously known as AB521, is a potent and selective small-molecule HIF-2α inhibitor that has shown tumour reduction in preclinical models.[14] Casdatifan binds to the PAS-B domain with high affinity and selectively disrupts HIF-2α from forming a heterodimer with **HIF-1β** and blocks HIF-2α-dependent gene expression that promotes tumour progression.[14,15] In vitro casdatifan exhibited minimal drug–drug interaction (DDI) potential, as it had no effect on inhibiting major CYP enzymes in vitro, and it only showed the potential to weakly induce **CYP3A4** enzyme.[16] In preclinical species, casdatifan exhibited low clearance and moderate to high oral bioavailability. In 28-day multiple-dose good laboratory practice toxicity studies in rats and dogs, casdatifan was well tolerated, without clinical signs in both species. The proposed first-in-human (FIH) starting dose of 3 mg of casdatifan (approximately 0.05 mg/kg in a 60-kg human) was selected to be safe based on the totality of nonclinical data, including toxicological and pharmacological considerations, allowing adequate safety margin consistent with International Council for Harmonization M3 guidance.[17]

The present study was a FIH clinical study designed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of orally administered casdatifan. The primary objectives of the study were to characterize the safety, tolerability and PK of casdatifan after single and multiple ascending doses of casdatifan in the single ascending dose (SAD) and multiple ascending dose (MAD) parts of the study. The secondary objective of the study was to evaluate the effect of DDI of multiple oral doses of casdatifan on the PK profile of **midazolam**, a probe substrate for the CYP3A4 enzyme. As part of the exploratory objectives of the study, the PD of casdatifan—in this case, reduction in serum EPO levels—and the urinary excretion of casdatifan were assessed.

What is already known about this subject

- Hypoxia-inducible factor (HIF)-2α is a transcription factor that is an oncogenic driver in clear cell renal cell carcinoma.
- HIF-2α inhibition disrupts several processes critical to tumour growth and survival, providing significant therapeutic effects.
- Casdatifan is a potent, selective and orally bioavailable inhibitor of HIF-2α.

What this study adds

- Casdatifan exhibits dose-linear and time-invariant pharmacokinetics in the dose range 3–100 mg with a half-life of approximately 24 h.
- Casdatifan elicited concentration-dependent reductions in erythropoietin levels, consistent with HIF-2α inhibition.
- Available pharmacokinetic/pharmacodynamic profile of casdatifan in healthy participants indicates a strong therapeutic potential as a HIF-2α inhibitor.

2 | METHODS

2.1 | Study design

This phase 1, FIH, single-centre study (NCT05117554) consisted of a double-blind, randomized, placebo-controlled SAD part and a double-blind, randomized, placebo-controlled MAD part to investigate the safety, tolerability and PK of oral doses of casdatifan (Figure 1). Blinding during the study was maintained by ensuring that investigators and participants were unaware of the treatment assignment, with treatments being provided in identical packaging and labelling. A third part of the study was a DDI part conducted as an open-label, fixed sequence, 2-period study to evaluate the effect of multiple oral doses of casdatifan on the PK of a single dose of midazolam. The study was

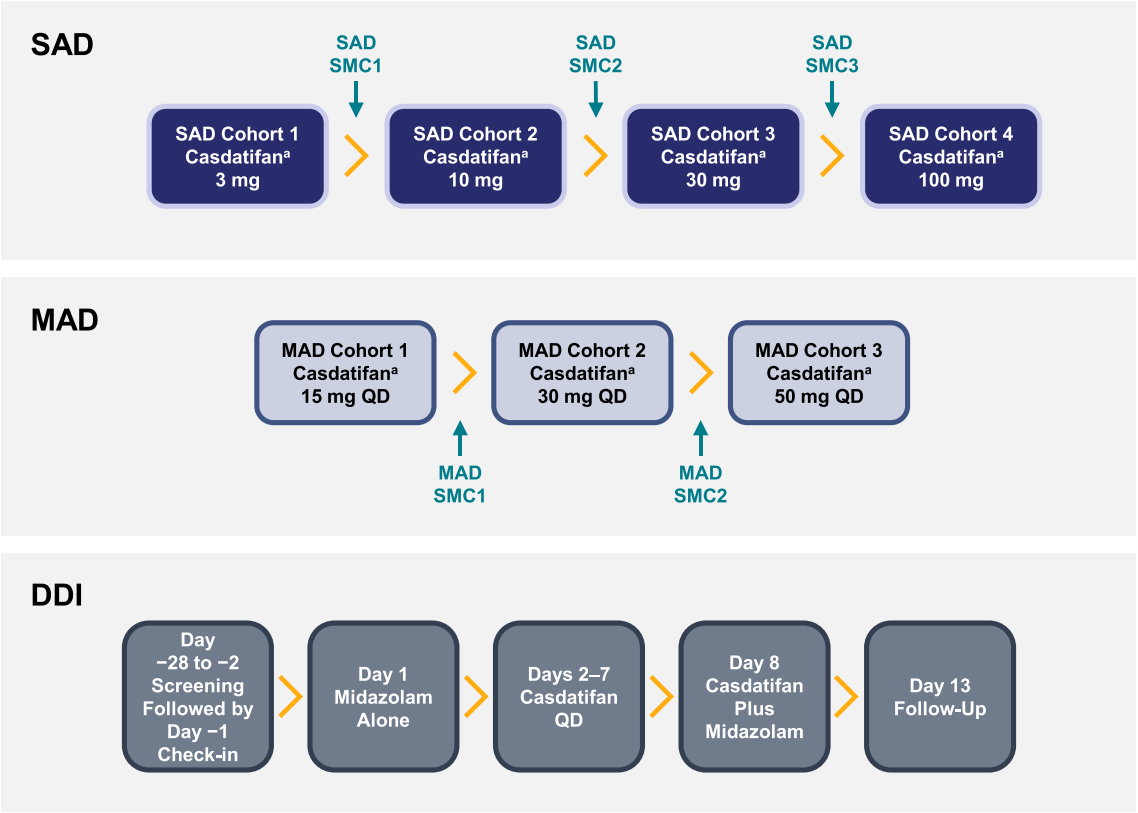

FIGURE 1 The schematics for each part of the study. DDI, drug–drug interaction; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose; SMC, safety monitoring committee. [a] In each SAD/MAD cohort, 8 participants were enrolled and received casdatifan or placebo in a 3:1 ratio. In the DDI cohort, 12 participants were enrolled.

conducted in accordance with International Council for Harmonization guidelines, applicable local laws, regulations and guidelines governing clinical study conduct and ethical principles that have their origin in Declaration of Helsinki. This study was approved by an independent ethics committee before its initiation. The study was conducted between November 2021 and February 2023 at ICON Early Clinical & Bioanalytical Solutions (Groningen, The Netherlands).

The SAD part included 4 cohorts of 8 healthy participants. For each cohort, a participant received a single oral dose of casdatifan or placebo and was randomized at an overall 3:1 ratio of casdatifan to placebo. Casdatifan or placebo was administered at least 4 h before or after meals or fluid intake.

The MAD part included 3 cohorts with a total of 26 healthy participants, of whom 24 completed all assessments. For each cohort, a participant received multiple oral doses of casdatifan or placebo once daily (QD) for 7 days and was randomized at a 3:1 ratio of active to placebo. Casdatifan (or placebo) was administered at least 4 h before or after meals or fluid intake on days 1 and 7 and 2 h before or after on days 2–6 to minimize any potential impact of food on drug absorption, while allowing for more flexibility on days 2–6, with no expected impact on EPO evaluations. MAD cohort 1 started following the completion of SAD cohort 4.

For this preliminary study, no prospective calculations of statistical power have been made. The sample size in SAD/MAD cohorts was deemed to be adequate to provide information on safety, tolerability, PK and PD following different doses of casdatifan, consistent with other similar FIH randomized studies.[18–20]

For the SAD/MAD parts, participants were admitted to the clinical unit on day −2. During the inclinic treatment period, participants stayed in the clinic until day 7 and day 8 for the SAD and MAD part, respectively, before being discharged, provided that, in the opinion of the principal investigator, there were no safety concerns. For the SAD cohorts, the post-clinic follow-up visits occurred on days 10 and 13, and the end-of-study (EOS) follow-up visit occurred between day 21 and day 28. For the MAD cohorts, post-clinic follow-up visits occurred on days 11, 14 and 17, and the EOS follow-up visit occurred between day 22 and day 25.

The DDI part included a cohort of 12 healthy participants. Participants were admitted to the clinical unit on day −1. Midazolam 2 mg was administered after an overnight fast of at least 10 h, which continued for 4 h postdose on day 1 when administered alone and on day 8 when coadministered with casdatifan. Casdatifan 50 mg (5 × 10-mg capsules) was administered at least 4 h before and after a meal and fluid on days 2 and 7 and at least 2 h before or after a meal and fluid on days 3–6.

During the SAD and MAD parts of the study, full profile (i.e., after the day 1 dose for SAD and day 1 and day 7 doses for MAD) and predose PK and PD samples at screening, baseline and on treatment days

were collected to characterize the PK and PD of casdatifan in healthy participants. Safety evaluations were also performed at screening, baseline and on treatment days (see the Supporting Information for details and results). Urine samples at different intervals were collected to characterize the urinary excretion of casdatifan. In the DDI part of the study, plasma samples were obtained at both periods when midazolam was administered alone and with casdatifan to characterize the full midazolam PK profile.

The analysis of casdatifan in plasma and urine samples was performed at Syneos Health (Princeton, NJ, USA) using validated liquid chromatography-mass spectrometry/mass spectrometry methods. The lower limit of quantification was 1 ng/mL for plasma concentrations. All quality control samples analysed during the study met the predefined acceptance criteria.

The analysis of midazolam and 1-hydroxymidazolam in plasma samples was performed at ICON Bioanalytical Laboratories (Whitesboro, NY, USA) using validated liquid chromatography-mass spectrometry/mass spectrometry methods. The lower limit of quantification was 0.05 ng/mL for midazolam and 1-hydroxymidazolam. All quality control samples analysed during the study met the predefined acceptance criteria.

To assess target engagement across the range of casdatifan doses evaluated in the study, we used EPO, a well-characterized, specific pharmacodynamic biomarker of HIF-2α inhibition.[12,13] EPO concentrations from serum samples collected before and after dosing of casdatifan or placebo in the SAD/MAD portion of the study were analysed at ICON Early Clinical & Bioanalytical Solutions (Groningen, The Netherlands) using the Immulite 2000 analyser (Siemens Healthineers, Cary, NC, USA) with 1.0 mIU/mL detection limit. Fit-for-purpose method validation to establish appropriate reproducibility, accuracy and precision of EPO measurements from serum were performed per manufacturer recommendations.

2.2 | Eligibility criteria

Eligible participants were healthy vasectomized male and healthy female volunteers aged ≥18 to <55 years, with body weights of ≥50 to ≤80 kg and body mass indices of ≥18.5 to <25.0 kg/m^2 to minimize potential body size impact on the observed PK exposures. Participants abstained from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) and alcohol from 48 h before the first casdatifan dose until after collection of the final PK and/or PD sample. Daily or regular use of tobacco products was not allowed from 3 months before screening until after the EOS follow-up visit. Based on preclinical reproductive toxicity studies in rats and dog, casdatifan had no effects on the female reproductive organs of rats and dogs when tested up to 13 weeks' duration. However, effects in male reproductive organs, including testes and epididymis, were observed in rats and did not fully recover during the 12-week postdose recovery periods. This is consistent with the preclinical toxicology data of belzutifan, another HIF-2α inhibitor.[21] Therefore, only healthy females and healthy vasectomized males were eligible for this study.

2.3 | PK analysis

The plasma PK parameters for casdatifan, midazolam and 1-hydroxymidazolam were obtained based on noncompartmental analyses of their respective concentration–time profiles, using Phoenix WinNonlin Version 8.2 (Certara USA, Princeton, NJ, USA).

The PK parameters estimated were maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration *vs.* time curve (AUC) from time zero to last quantifiable concentration ($AUC_{0\text{-last}}$), AUC from time zero to infinity ($AUC_{0\text{-inf}}$), apparent oral clearance, apparent volume of distribution at terminal elimination phase and/or terminal phase half-life ($t_{1/2}$) for casdatifan and midazolam and its metabolite, 1-hydroxymidazolam. In addition, AUC for the dosing interval ($AUC_{0\text{-tau}}$), and $AUC_{0\text{-tau}}$ accumulation ratio, amount excreted in urine from time zero to time t, fraction of the administered dose excreted in urine as unchanged drug (F_e) and renal clearance (CL_R) were calculated for casdatifan. The AUC calculations were done using the linear-logarithmic trapezoidal option in Phoenix WinNonlin.

Dose proportionality for casdatifan in the SAD and MAD parts was explored using a regression (power) model relating natural log-transformed PK parameters,

$$\ln(\mathrm{PK}) = \ln(\beta_0) + \beta_1 \cdot \ln(\mathrm{dose}) + \varepsilon,$$

where PK is the PK parameter tested (e.g., C_{max} or AUC), $\ln(\beta_0)$ is the y-intercept, β_1 is the slope (a β_1 value of 1 indicates linearity) and ε is an error term. A point estimate and 95% confidence intervals (CIs) were produced for the slope. A slope of 1 (i.e., a 95% CI containing 1) indicated that no evidence of a deviation from dose proportionality was found.

For the DDI part, the effect of multiple oral doses of casdatifan on the single-dose PK of midazolam and 1-hydroxymidazoam was assessed. The effect of casdatifan on the natural log-transformed C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of midazolam and 1-hydroxymidazolam was assessed with a linear mixed-effects model. Treatment (combined casdatifan + midazolam as test treatment *vs.* single midazolam treatment as reference treatment) was used as a fixed effect, and the participant was used as a random effect. The back-transformed (i.e., exponentiated) least squares mean for each treatment and ratio with 90% CI were estimated in this model.

2.4 | PD analysis

Longitudinal concentrations of EPO were determined for each participant and normalized to the baseline EPO value to obtain each participant's percent change from baseline. EPO values below the limit of detection of the EPO assay (i.e., 1 mIU/mL) were imputed to 0.9 mIU/mL. The analysis of group-by-time interaction was performed in R using a nonparametric rank-based mixed model using a Wald-type statistic. Only complete data sets ($n = 51$ out of 56; 91%) were included in the analysis. To follow-up on interactions, Kruskal–Wallis or Friedman tests were performed, followed by pairwise Wilcox Rank

Sum or Wilcoxon signed rank tests where appropriate in Graph Pad Prism, adjusting for multiple comparisons with the Benjamini, Krieger and Yekutieli method.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.[22,23]

3 | RESULTS

3.1 | Participant disposition

Seventy female participants were included in the study and received study drug: 32 participants (8 placebo; 24 casdatifan) in the SAD part, 26 participants (6 placebo; 20 casdatifan) in the MAD part and 12 participants in the DDI part. Although vasectomized males could also be included, none were found to be eligible for the study. Mean age and total body weight ranged from 22–28 years and 70–80 kg for the SAD part cohorts and 27–37 years and 70–80 kg for the MAD part cohorts, respectively. For the DDI part, the mean age and total body weight were 28 years and 78 kg, respectively. Most participants self-reported as White, and all had child-bearing potential.

Of the 70 female participants included, 68 completed the study while 2 withdrew for personal reasons. One participant withdrew from the study on day 1 after receiving the first dose of 15 mg, and 1 participant withdrew from the study on day 3 after receiving the first 2 doses of 50 mg casdatifan. There were no treatment-emergent adverse events (TEAEs) leading to study drug discontinuation. All participants were included in safety and/or PD datasets in different parts of the study. Furthermore, all participants who received casdatifan were included in the PK dataset with the exception of the participant who withdrew from the study on day 1.

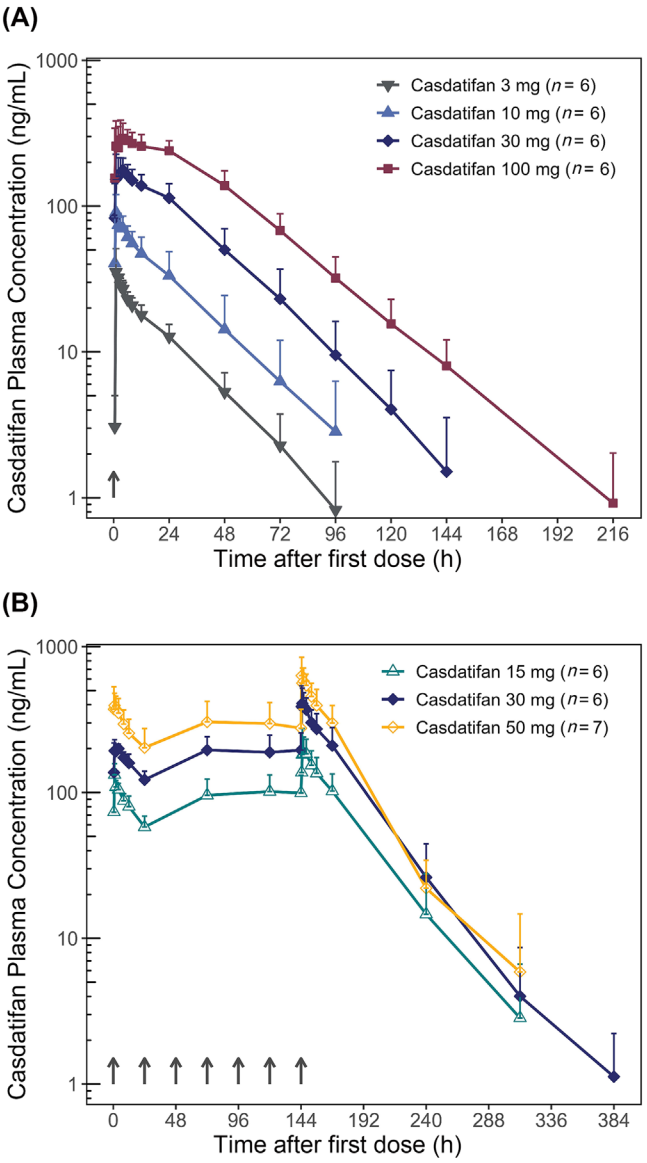

FIGURE 2 Mean (+standard deviation) casdatifan plasma concentration–time profiles in the (A) single ascending dose and (B) multiple ascending dose parts of the study. Vertical upward arrows indicate casdatifan dosing events.

3.2 | PK

3.2.1 | SAD/MAD parts

After single or multiple oral dosing, casdatifan was rapidly absorbed into the systemic circulation with T_{max} between 1 and 4 h postdose (Figure 2). After 3–100 mg single oral doses and 15–50 mg multiple once daily dosing, the respective geometric mean casdatifan plasma C_{max} and $AUC_{0\text{-inf}}$ increased with dose, with geometric mean $t_{1/2}$ of 17–25 h (Tables 1 and 2). After multiple doses, steady-state casdatifan concentrations were reached by day 4 (Figure 2). With QD dosing, the geometric mean accumulation ratio ranged from 1.52 to 1.75 for AUC over the 15–50 mg dose range (Table 2).

A dose-proportionality assessment was conducted by combining the SAD and MAD data. Casdatifan exposure (AUC and C_{max}) increased approximately dose proportionally over a single dose of 3–100 mg and over multiple doses of 15–50 mg QD (Figure S1). The point estimate of the slope was 0.82 for $AUC_{0\text{-tau}}$ at day 1 and 0.87 for combined data on $AUC_{0\text{-inf}}$ in SAD with $AUC_{0\text{-tau}}$ at steady-state (day 7) in MAD, with the 95% CIs being 0.74–0.89 and 0.78–0.96, respectively (Table S1).

Following single dosing with casdatifan 100 mg, the geometric mean for a fraction of the dose excreted in urine (Fe_{urine}) was 19.9% based on 144 h of collection. Following multiple dosing with casdatifan, the geometric mean Fe_{urine} within 24 h after dosing ranged from 25.9 to 34.2% on day 7 over the dose range of 15–50 mg (Table 2).

TABLE 1 Casdatifan plasma pharmacokinetic parameters—single ascending dose part.

Parameter, geometric mean (range)	Casdatifan 3 mg ($n = 6$)	Casdatifan 10 mg ($n = 6$)	Casdatifan 30 mg ($n = 6$)	Casdatifan 100 mg ($n = 6$)
C_{max} (ng/mL)	38.7 (29.5–57.5)	91.4 (56.7–136)	185 (139–274)	328 (249–473)
T_{max}[a] (h)	1.02 (1.00–2.00)	1.00 (0.50–6.00)	3.00 (1.00–6.00)	3.54 (0.50–6.07)
$AUC_{0\text{-last}}$ (ng h/mL)	748 (485–1061)	1947 (940–3637)	6365 (4228–8725)	14 734 (10 240–19 981)
$AUC_{0\text{-inf}}$ (ng h/mL)	801 (542–1138)	1995 (963–3687)	6424 (4254–8901)	14 847 (10 339–20 094)
CL/F (L/h)	3.75 (2.64–5.53)	5.01 (2.71–10.4)	4.67 (3.37–7.05)	6.74 (4.98–9.67)
V_z/F (L)	107 (95.2–124)	120 (87.8–152)	121 (95.9–158)	230 (202–285)
$t_{1/2}$ (h)	19.8 (15.2–25.0)	16.6 (9.13–30.2)	18.0 (15.5–25.3)	23.7 (20.4–29.2)

Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma concentration *vs.* time curve (AUC) from time 0 to infinity; $AUC_{0\text{-last}}$, AUC from time 0 to last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, half-life; T_{max}, time to C_{max};. V_z/F, apparent volume of distribution.

[a] For T_{max}, the median (range) is presented instead of geometric mean (range).

TABLE 2 Casdatifan plasma and urine pharmacokinetic parameters—multiple ascending dose part (PK set).

Parameter, geometric mean (range)	Analysis day	Casdatifan 15 mg QD ($n = 6$)	Casdatifan 30 mg QD ($n = 6$)	Casdatifan 50 mg QD ($n = 6$)
C_{max} (ng/mL)	Day 1	130 (104–165)	222 (190–293)	424 (323–560)[a]
C_{max} (ng/mL)	Day 7	194 (125–290)	431 (276–560)	647 (445–839)
T_{max}[b] (h)	Day 1	1.00 (1.00–1.00)	2.51 (0.50–12.02)	1.00 (0.52–2.02)[a]
T_{max}[b] (h)	Day 7	1.54 (1.00–4.00)	1.01 (0.50–4.00)	0.53 (0.50–3.98)
$AUC_{0\text{-tau}}$ (ng h/mL)	Day 1	1933 (1644–2380)	3669 (3214–4150) ($n = 5$)[c]	6352 (5431–10 209)[a]
$AUC_{0\text{-tau}}$ (ng h/mL)	Day 7	3236 (2097–4539)	6654 (4748–9231)	9777 (6871–13 416)
R_{ac} C_{max}	Day 7	1.49 (0.76–2.23)	1.94 (1.27–2.51)	1.52 (1.02–2.24)
R_{ac} AUC	Day 7	1.67 (1.07–2.33)	1.75 (1.26–2.22) ($n = 5$)[c]	1.52 (1.17–2.35)
CL/F (L/h)	Day 7	4.64 (3.30–7.15)	4.51 (3.25–6.32)	5.11 (3.73–7.28)
V_z/F (L)	Day 7	169 (127–191)	164 (143–186)	165 (139–191)
$t_{1/2}$ (h)	Day 7	25.3 (18.4–40.1)	25.3 (18.4–33.1)	22.3 (16.5–35.5)
$F_{e\ urine}$ (%)	Day 1	18.1 (4.4)	14.0 (2.0)	15.0 (2.1)[a]
$F_{e\ urine}$ (%)	Day 7	34.2 (11.1)	30.4 (7.3)	25.9 (3.8)
CL_R[d] (mL/min)	Day 1	22.8 (16.5–30.8)	19.9 (17.7–25.0) ($n = 5$)[e]	19.5 (11.1–25.3)[a]
CL_R[d] (mL/min)	Day 7	25.2 (18.5–33.8)	22.3 (15.6–27.8)	21.8 (16.4–30.0)

Abbreviations: Ae_{tau}, cumulative amount excreted in urine during the dosing interval; $AUC_{0\text{-tau}}$, area under the plasma concentration *vs.* time curve for the dosing interval; CL/F, apparent oral clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; $F_{e\ urine}$, fraction of the administered dose excreted unchanged into urine; PK, pharmacokinetic; QD, once daily; R_{ac}, $AUC_{0\text{-tau}}$ accumulation ratio; $t_{1/2}$, half-life; T_{max}, time to C_{max}; V_z/F, apparent volume of distribution.

[a]PK results on day 1 were available for 7 participants, and, on day 7, PK results were available for 6 participants since 1 participant withdrew from the study on day 3 after receiving the first 2 doses of 50 mg casdatifan on days 1 and 2.

[b]For T_{max}, the median (range) is presented instead of geometric mean (range).

[c]$AUC_{0\text{-tau}}$ was available on day 1 for 5 participants since $AUC_{0\text{-tau}}$ could not be estimated for 1 participant.

[d]For day 1, CL_R is calculated as Ae_{0-24}/AUC_{0-24}, and for day 7, CL_R is calculated as Ae_{tau}/AUC_{tau}, where tau = 24 h.

[e]CL_R was available on day 1 for 5 participants since $AUC_{0\text{-tau}}$ could not be estimated for 1 participant.

Note: For day 1, urine recovery is incomplete, and the results are based on the 24-h collection interval after dosing; thus, underestimating the fraction of dose excreted in urine as an unchanged drug.

3.2.2 | DDI part

Coadministration of midazolam and casdatifan resulted in approximately 23, 38 and 38% decrease in geometric mean value for midazolam C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, as compared with midazolam alone, respectively (Figure 3 and Table 3). This observation is similar to the magnitude of CYP3A4 DDI effect between midazolam and belzutifan.[10,21] Furthermore, the geometric mean of

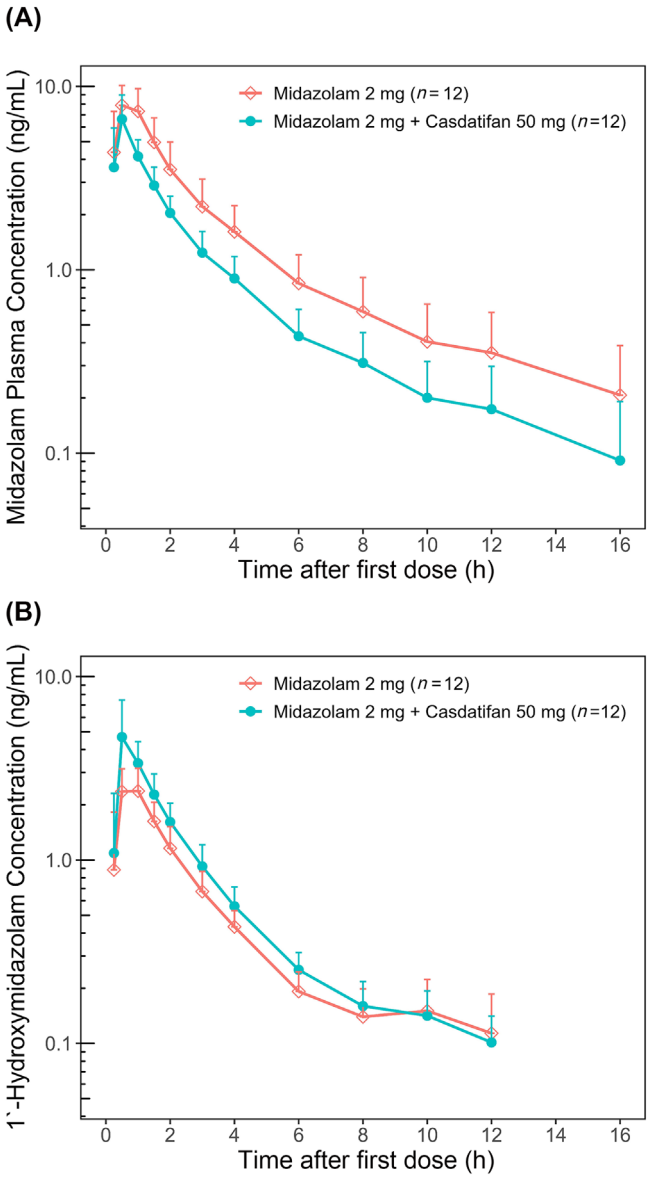

FIGURE 3 Mean (+standard deviation) (A) midazolam and (B) 1-hydroxymidazolam plasma concentration–time profiles following administration of midazolam alone and with casdatifan.

1-hydroxymidazolam C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ increased by approximately 66, 38 and 36% when midazolam was coadministered with casdatifan as compared with administration of midazolam alone.

TABLE 3 Midazolam and 1-hydroxymidazolam plasma pharmacokinetic parameters—drug–drug interaction part.

PK parameter, geometric mean (range)	Midazolam 2 mg (reference) Day 1 ($n = 12$)	Casdatifan 50 mg + midazolam 2 mg (test) Day 8 ($n = 12$)
	Midazolam	
C_{max} (ng/mL)	8.32 (5.32–12.7)	6.44 (3.60–10.2)
T_{max}[a] (h)	0.50 (0.25–1.00)	0.50 (0.50–1.00)
$AUC_{0\text{-last}}$ (ng h/mL)	21.5 (8.65–35.3)	13.2 (8.37–20.2)
$AUC_{0\text{-inf}}$ (ng h/mL)	22.3 (8.96–36.8)	13.8 (8.73–20.6)
$t_{1/2}$ (h)	4.40 (2.73–7.51)	4.15 (2.25–7.89)
	LS geometric mean ratio for test/reference (90% CI)[b]	
C_{max} ratio day 8/day 1	0.77 (0.48–1.71)	
$AUC_{0\text{-last}}$ ratio day 8/day 1	0.62 (0.44–1.59)	
$AUC_{0\text{-inf}}$ ratio day 8/day 1	0.62 (0.45–1.58)	
	1-Hydroxymidazolam	
C_{max} (ng/mL)	2.67 (1.61–4.13)	4.43 (1.56–9.63)
T_{max}[a] (h)	0.50 (0.25–1.00)	0.50 (0.50–1.00)
$AUC_{0\text{-last}}$ (ng h/mL)	6.21 (3.93–8.52)	8.60 (5.64–13.4)
$AUC_{0\text{-inf}}$ (ng h/mL)	6.66 (4.13–8.89)	9.03 (6.00–14.0)
$t_{1/2}$ (h)	3.29 (1.84–7.39)	3.43 (2.02–6.99)
MR C_{max}	0.31 (0.21–0.52)	0.66 (0.41–1.02)
MR $AUC_{0\text{-last}}$	0.28 (0.19–0.44)	0.62 (0.30–1.07)
MR $AUC_{0\text{-inf}}$	0.29 (0.20–0.47)	0.63 (0.30–1.05)
	LS geometric mean ratio for test/reference (90% CI)[b]	
C_{max} ratio day 8/day 1	1.66 (0.91–3.19)	
$AUC_{0\text{-last}}$ ratio day 8/day 1	1.38 (0.90–2.57)	
$AUC_{0\text{-inf}}$ ratio day 8/day 1	1.36 (0.91–2.51)	

Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma concentration *vs.* time curve (AUC) from time 0 to infinity; $AUC_{0\text{-last}}$, AUC from time 0 to last quantifiable concentration; ANOVA, analysis of variance; C_{max}, maximum plasma concentration; LS, least squares; MR, metabolite to parent ratio; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max}, time to C_{max}.

[a]For T_{max}, the median (range) is presented instead of geometric mean (range).

[b]Drug-drug interaction was assessed in an ANOVA model with treatment as fixed effect and participant as random effect.

3.3 | PD

3.3.1 | SAD/MAD parts

In the SAD part, baseline mean EPO levels ranged from 2.51 to 12.7 mIU/mL. In comparison to the placebo group, reductions in EPO levels were apparent following a single dose of casdatifan at doses of 10 mg or higher (Figure 4). The decrease was dose- and time-dependent and was more pronounced and statistically significant for the higher casdatifan doses of 30 and 100 mg, reaching the lowest mean serum EPO levels at 24 h postdose (Table 4). Although all groups, including placebo, showed elevations of EPO that were statistically significant relative to baseline at later time points (Table S2), the groups did not differ, including at the latest time point assessed (Table 4). Time required for EPO to return to baseline was dose dependent, consistent with the PK profile.

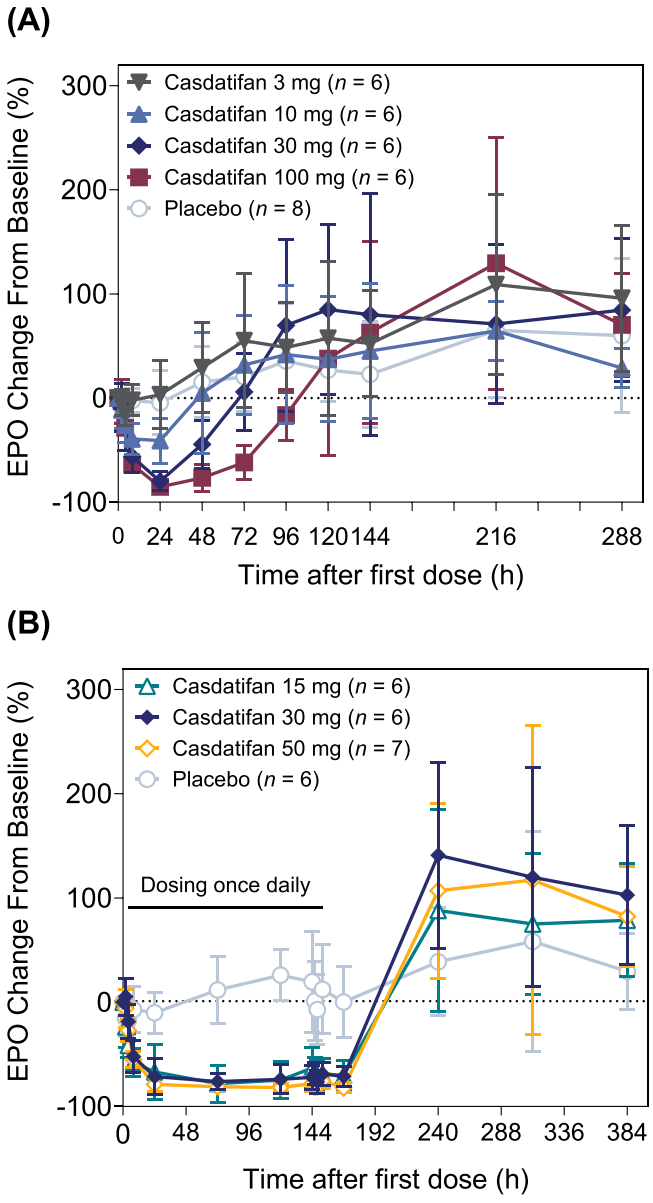

FIGURE 4 Mean (±standard deviation) change from baseline serum erythropoietin level over time in the (A) single ascending dose and (B) multiple ascending dose parts of the study.

In the MAD part, baseline mean EPO levels ranged from 3.39 to 21.7 mIU/mL. Following multiple dosing with casdatifan, mean serum EPO levels decreased rapidly at all 3 dose levels, reaching the lowest levels by day 4 (i.e., 72 h after the first dose) and remained suppressed throughout the dosing period (Figure 4). This decrease in serum EPO levels was statistically significant ($P < .05$) for all 3 casdatifan dose levels (Table 4) when compared with the placebo group. As shown in Figure 4, mean serum EPO levels appeared to rebound to greater than baseline levels by day 11 (i.e., 240 h after the first dose; 96 h after the last dose) and remained elevated on day 17 (i.e., 384 h after the first dose; 240 h after the last dose). The rebound observed at the later time points was significant in all the casdatifan-treated groups in contrast to the placebo group (Table S3). However, none of the casdatifan groups differed significantly (Table 4), nor was the observed EPO rebound associated with any safety signal through EOS visit (see Safety section).

The relationship between casdatifan average steady-state plasma concentration, calculated as day 7 $AUC_{0\text{-}tau}$ divided by 24 h, and EPO percent change from baseline at day 8, 24 h after dosing on day 7, was explored using a baseline Imax model; it showed concentration-dependent reductions in EPO reaching near maximal reduction from baseline of approximately 80% at an average casdatifan concentration of 400 ng/mL (Figure 5). Based on the PK/PD model predictions, casdatifan dose of 20 mg QD is expected to provide >70% reduction in EPO levels from baseline, which is higher than the reported mean level of EPO suppression observed with belzutifan 120 mg daily in patients with von Hippel–Lindau disease-associated RCC (VHL-RCC), RCC or solid tumours (64%).[24]

3.4 | Safety

3.4.1 | SAD/MAD parts

In the SAD part, a total of 74 TEAEs were reported by 28 (87.5%) of 32 participants. All 74 TEAEs were mild. There was no relationship with casdatifan dose level or a clear difference between the casdatifan dose levels and placebo with regard to the percentage of participants reporting TEAEs or the number of TEAEs. Most TEAEs had resolved without sequelae by the EOS follow-up visit.

In the MAD part, a total of 98 TEAEs were reported by 24 (92.3%) of 26 participants. A total of 23 TEAEs reported by 12 (46.2%) of 26 participants were considered by the principal investigator to be related to the study drug; 18 TEAEs reported by 9 (45.0%) of 20 participants receiving casdatifan, and 5 TEAEs reported by 3 (50.0%) of 6 participants receiving placebo. There were no deaths and no serious adverse events reported. No clear change in the percentage of participants reporting TEAEs was observed over the casdatifan dose range (100, 100 and 85.7% of participants receiving multiple oral doses of 15, 30 or 50 mg casdatifan, respectively) in comparison with placebo (83.3%). A total of 94 of the 98 TEAEs were mild, and the remaining 4 TEAEs were moderate (3 TEAEs of headache [1 TEAE in placebo] and 1 TEAE of gastrointestinal disorder). Most TEAEs had resolved without sequelae by the EOS follow-up visit. The most common (≥5%) treatment-related TEAEs by preferred term were headache (8 participants, 30.8%), dizziness (4 participants, 15.4%), nausea (3 participants, 11.5%), abdominal pain (1 participant, 3.8%) and diarrhoea (1 participant, 3.8%).

3.4.2 | DDI part

A summary of safety data for the DDI part of the study can be found in the Supporting Information.

TABLE 4 Arithmetic mean percent change from baseline in erythropoietin levels following single and multiple doses of casdatifan.

Study part	Dose	*n*	EPO change from baseline, % (± SD)		
			24 h after day 1 dose	24 h after day 7 dose	Last PD time point [a]
SAD	Placebo	8	−5 ± 31	NA	60 ± 74
	Casdatifan 3 mg	6	3 ± 33	NA	96 ± 70
	Casdatifan 10 mg	6	−41 ± 22	NA	29 ± 18
	Casdatifan 30 mg	6	−80 ± 9**	NA	85 ± 69
	Casdatifan 100 mg	6	−85 ± 4***	NA	70 ± 50
MAD (QD for 7 days)	Placebo	6	−10 ± 20	0 ± 34	30 ± 36
	Casdatifan 15 mg	6	−67 ± 27**	−70 ± 14*	79 ± 54
	Casdatifan 30 mg	6	−71 ± 18**	−72 ± 10*	103 ± 67
	Casdatifan 50 mg	6	−79 ± 7**	−83 ± 5***	82 ± 48

Abbreviations: EPO, erythropoietin; MAD, multiple ascending dose; NA, not applicable; QD, once daily; SAD, single ascending dose; SD, standard deviation. Kruskal–Wallis to test overall differences between groups, followed by pairwise Wilcox Rank Sum tests adjusting for multiple comparisons with the Benjamini, Krieger and Yekutieli method. $P < .05$*, $P < .01$**, or $P < .001$***, significant difference compared with the placebo group.
[a]SAD day 13 (288 h after the first dose), MAD day 17 (384 h after the first dose). In addition, differences were not observed at SAD day 10 (216 h after the first dose), or MAD day 11 or day 14 (240 h or 312 h, respectively after the first dose) (data not shown).

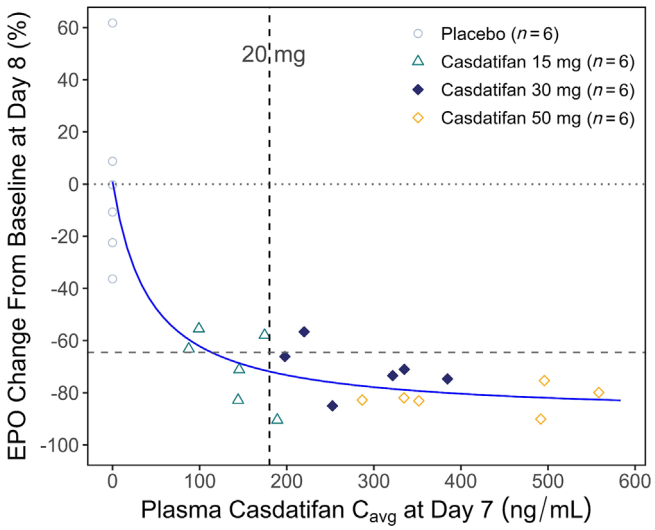

FIGURE 5 Relationship between the percent change from baseline in serum EPO levels at day 8 and casdatifan average plasma concentration at day 7 in the multiple ascending dose part of the study. Solid blue line indicates predictions of PK/PD relationship, using a baseline I_{max} model. Effect $= E_0 + (I_{max} \times C_{avg}) / (IC_{50} + C_{avg})$ fitted with nonlinear least squares approach: I_{max} fixed to −90%, $E_0 = 0.948\%$ (with standard deviation = 6.47%), $IC_{50} = 42.5$ ng/mL (with standard deviation = 26.0 ng/mL) and residual standard error = 18.3 on 22 degrees of freedom. Vertical black dashed line indicates casdatifan plasma C_{avg} at daily dose of 20 mg, and horizontal grey dashed line indicates EPO% change from baseline for belzutifan at 120 mg QD (about −64%).[24] C_{avg}, average concentration; EPO, erythropoietin; PD, pharmacodynamics; QD, once daily.

3.4.3 | Electrocardiogram, laboratory and vitals

No changes or trends of clinical significance were seen for heart rate, PR interval, RR interval, QRS duration, uncorrected QT interval, or QTcF interval during any of the study parts. All 12-lead electrocardiogram evaluations were recorded as normal or, in case of abnormal recordings, were not considered clinically significant. In the SAD part, no participants who received casdatifan experienced a QTcF > 450 ms or ΔQTcF > 30 ms. In the MAD part, there was 1 participant with QTcF > 450 and ≤480 ms or ΔQTcF > 30 ms (mild). No participants experienced a QTcF > 480 ms or ΔQTcF > 30 ms. A scatter plot of the estimated placebo-adjusted ΔQTcF (pooled SAD and MAD) *vs.* casdatifan plasma concentration indicates a lack of QTcF prolongation with casdatifan administration given the upper bound of the 90% CI is <10 ms (Figure S2).

Although several individual changes from baseline in laboratory values were observed, no clinically important trends were seen during any part of the study. In all study parts, clinical safety laboratory tests outside of normal range values were observed at various times. However, these were minor and, in all cases, considered by the principal investigator to have no clinical significance.

Although several individual changes from baseline were observed in vitals such as blood pressure, pulse rate, body temperature, respiratory rate and oxygen saturation, no trends or clinically relevant changes were observed during any part of the study.

4 | DISCUSSION

In this phase 1, FIH clinical study, a combined analysis of the SAD and MAD parts of the study demonstrated a dose-proportional increase in AUC of casdatifan in healthy participants across the tested dose range and linear PK after multiple dosing. Dose proportionality in exposure will allow testing of higher doses, and a $t_{1/2}$ of approximately 24 h is consistent with the intended once-daily dosing of this molecule in future clinical trials. Higher doses were not tested in this study to minimize toxicity (e.g., hypoxia, anaemia) considering lack of potential

benefit in healthy participants. Furthermore, the combined PK/PD analysis (Figure 5) provided a safe and biologically active starting dose level of 20 mg QD for first-in-cancer patient study of ARC-20 (NCT05536141), a phase 1 study in patients with solid tumours. The totality of PK/PD data from this study indicates that a dose of 20 mg casdatifan would result in ~70% reduction from baseline EPO, which is similar to the observation in patients with belzutifan 120 mg QD,[24] the only approved compound targeting HIF-2α. However, belzutifan shows limited increase in exposure above the approved dose of 120 mg.[12,25] In contrast, the observed dose-linear PK profile of casdatifan has resulted in further increases in plasma exposures with higher doses resulting in greater EPO reduction (~85% in healthy volunteers, Table 4), and ~80% in patients with ccRCC,[26,27] potentially maximizing the therapeutic potential of HIF-2α inhibition in cancer patients (ccRCC).

As expected, due to the on-target pharmacological effect of casdatifan, decreases in serum EPO levels were observed following the administration of casdatifan after single and multiple doses. A dose- and concentration-dependent reduction in EPO levels was observed, consistent with targeting the HIF-2α pathway. Daily doses of 30 and 50 mg resulted in mean EPO reductions of 72–83% by day 8, indicating that doses in the tested range are more potent at modulating the HIF-2α pathway than 120 mg belzutifan, which was reported to cause 64% mean EPO reduction at steady state.[24] However, the reported belzutifan data are from studies conducted in patients VHL-RCC and ccRCC, whereas this study was conducted in healthy participants. As the primary source of EPO production is normal kidney,[28–30] comparing the observed casdatifan EPO effect from the current study to data reported for belzutifan[24] is relevant. Preliminary data also indicate that casdatifan-mediated EPO inhibition is similar in patients with ccRCC[26,27] compared with healthy participants reported in this study. Combined with the linear PK profile of casdatifan in the dose range of 30–100 mg daily, higher doses of casdatifan enable evaluation of the full therapeutic potential of targeting the HIF-2α pathway in patients with cancer. Overall, the exceptional PK/PD profile of casdatifan highlights the strong therapeutic potential of this molecule.

As elevations of EPO above baseline levels at later time points were observed in placebo and casdatifan dosed participants (Figure 4), the rebound appears to be due to multiple factors, including an increase in EPO production due to study-related blood sample draws for PK, PD and safety[31–33] and a re-emergence of HIF-2α activity after casdatifan discontinuation. In SAD cohorts, the placebo-treated group as well as casdatifan-dosed groups showed statistically significant elevation of EPO over baseline at later time points (Table S2). In comparison, in MAD cohorts with an extended HIF-2α inhibition for >7 days, EPO rebound was significant in all casdatifan-dosed groups in a dose-dependent manner, with the higher casdatifan dose groups showing increased statistical significance (Table S3). In addition, the observed EPO rebounds, in both SAD and MAD cohorts, were not associated with any safety concern, including as evaluated at EOS follow-up visits.

Consistent with in vitro findings, coadministration of casdatifan with midazolam, a sensitive CYP3A4 substrate, reduced midazolam exposure. The magnitude of the reduction indicates that casdatifan is a weak CYP3A4 inducer at the tested doses, similar to belzutifan.[10,21] Therefore, casdatifan can be coadministered with other drugs that are CYP3A4 substrates without dose adjustments. This is important as vascular endothelial growth factor receptor tyrosine kinase inhibitors (e.g., cabozantinib, an existing standard of care in ccRCC) are CYP3A4 substrates.[34]

Following multiple dosing of casdatifan, approximately 26–34% of the administered casdatifan dose at 15–50 mg QD was excreted in the urine as an unchanged drug. Approximately 30% of the overall clearance of casdatifan appears to be via the kidney, indicating that renal clearance is potentially a minor elimination pathway for casdatifan. Therefore, the PK of casdatifan is unlikely to be affected to a clinically significant extent in participants with mild or moderate renal impairment. The urine PK data support the inclusion of patients with mild-to-moderate renal impairment in future clinical trials, which will allow a broad range of patients with ccRCC to benefit from this experimental therapy as many patients with ccRCC have impaired renal function.

A key characteristic of this study is that it was conducted in healthy participants, allowing for a controlled FIH assessment of the PK, PD and safety profile before advancing to studies in patients with cancer. EPO is an on-target PD biomarker measuring target inhibition in kidney.[30] The exact relationship between the extent of EPO suppression and disease endpoints is not yet known for this mechanism of action; however, greater EPO reduction is indicative of stronger HIF-2α pathway inhibition that could result in improved tumour efficacy. Based on the current study, casdatifan dose of 20 mg QD was selected to be the starting dose for dose escalation in patients with cancer (NCT05536141). This dose was expected to be safe and well tolerated, providing a similar level of EPO suppression (60–70%) in patients as belzutifan 120 mg QD (benchmark peripheral PD[24]). The intent of casdatifan dose escalation in cancer patients was to confirm the PK, EPO peripheral PD and safety profile of higher doses of casdatifan and identify the recommended dose for expansion. Preliminary data indicate that the PK and EPO peripheral PD profile of casdatifan in healthy participants and patients with cancer are similar.[26,27] Furthermore, preliminary casdatifan safety and efficacy data from patients with cancer (NCT05536141) confirm the therapeutic potential of casdatifan in ccRCC.[35]

In conclusion, data from single and multiple dosing of casdatifan in healthy participants support a PK and PD profile consistent with a strong therapeutic potential for this molecule. Combined with emerging efficacy and safety data, casdatifan monotherapy in patients with ccRCC has the potential to be a key component of the therapeutic strategy for treating ccRCC. In addition, healthy participant studies for cancer molecules can rapidly provide valuable PK and PD data that inform dose selection for studies in patients with cancer and minimize the number of patients with cancer receiving subtherapeutic doses, provided that the safety profile of the drug being investigated is not a concern for healthy participants.

AUTHOR CONTRIBUTIONS

Mohammad Ghasemi, Ji Yun Kim, Lisa Seitz, Lixia Jin, Paul Foster, Kai Liao, Tzuling Cheng, Elaine Paterson, Nicole Rosario, Reza Khosravan and Balaji Agoram contributed to the design, analysis and interpretation of the study. Maria Velinova conducted the study and contributed to the analysis and interpretation of the data. Mohammad Ghasemi wrote the first draft of the manuscript. All authors critically reviewed and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

M.G., J.K., L.S., L.J., P.G.F., N.R.R., R.K. and B.A. are full-time employees of Arcus Biosciences, Inc. and may own stock and/or stock options. K.H.L., T.C. and E.P. are former employees of Arcus Biosciences and may own stock and/or stock options. M.V. is a full-time employee of ICON Early Clinical & Bioanalytical Solutions.

DATA AVAILABILITY STATEMENT

Arcus Biosciences is committed to responsible sharing of data from clinical trials we sponsor. This includes summary and de-identified individual participant data, as well as other trial information (protocols, statistical analysis plans and clinical study reports). Requests for data from any qualified researcher who engages in rigorous, independent scientific research will be considered if the clinical trial data are not part of an ongoing or planned regulatory submission. Original data will be available for 12 months, beginning 3 months after approval of the study drug for use in patients or a new indication. For information on the process or to submit a request, visit https://trials.arcusbio.com/our-transparency-policy.

PATIENT CONSENT STATEMENT

All participants provided written informed consent.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov, NCT05117554.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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