HIF-2α is a Clinical Stage, Potent, and Selective Hypoxia-Inducible Factor (HIF)-2α Inhibitor, for the Treatment of Renal Cell Carcinoma

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AB521, a Clinical Stage, Potent, and Selective Hypoxia-Inducible Factor (HIF)-2α Inhibitor, for the Treatment of Renal Cell Carcinoma

The master transcriptional regulators of hypoxia-induced genes are HIF-1α and HIF-2α.

Preclinical and clinical evidence suggests that HIF-2α is a key driver of tumor progression and angiogenesis in RCC. HIF-2α potently inhibits HIF-2α-dependent transcription in RCC xenografts.

HIF-2α inhibits the transcription of various gene sets, some of which are pro-tumorigenic, downstream of hypoxia-inducible gene expression.

AB521 is currently under clinical evaluation (ARC-14) in healthy volunteers to reexamine the relationship between pharmacokinetics and pharmacodynamics of AB521 in pharmacologically relevant conditions.

AB521 is highly selective for HIF-2α and demonstrates excellent oral bioavailability in preclinical species.

AB521 is a novel and potent small molecule inhibitor of HIF-2α, which blocks HIF-2α-mediated gene transcription under physiologically relevant conditions.

AB521 selectively inhibits HIF-2α gene transcription with IC50 values of 33 and 28 nM, respectively.

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SUMMARY

AB521 is a novel and potent small molecule inhibitor of HIF-2α, which blocks HIF-2α-mediated gene transcription under physiologically relevant conditions.

AB521 is highly selective for HIF-2α.

AB521 exhibits a favorable pharmacodynamic profile in preclinical models with minimal direct or time-dependent inhibition of major CYP isoforms.

AB521 significantly inhibits tumor growth, and enhanced tumor killing activity was observed when administered in combination with the TKI cabozantinib.

Emerging healthy volunteer data projects that AB521 will possess a human pharmacokinetic profile suitable for once-daily dosing.

CITATIONS