Translational Analysis of RVT-1201 Nonclinical and Clinical Pharmacokinetic and Pharmacodynamic Biomarker Data to Predict Clinical Dose of a Novel TPH Inhibitor for Treatment of Pulmonary Arterial Hypertension

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BACKGROUND

Pulmonary arterial hypertension (PAH) is a progressive disorder associated with increased pulmonary vascular resistance, remodeling and occlusion. While etiology is unknown, nonclinical and clinical data implicate a causative role for serotonin.

RVT-1201 (previously KAR5585), is an oral prodrug for KAR5417 - a potent inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the peripheral biosynthesis of serotonin.

Here we report translation of PK/PD relationships for KAR5417 exposure and serotonin biomarker pharmacodynamics, to a human dose for treatment of PAH.

In rat, RVT-1201 at 100 mg/kg/day, (~50% reduction in serotonin biosynthesis) ameliorates PAH in both a monocrotaline prevention model and a SUGEN-hypoxia treatment model of established PAH.

In healthy humans (n=~120) receiving RVT-1201 across 2 studies:

- Treatment emergent adverse events resolved, none were serious, nor considered a dose limiting toxicity.
- With standard meals, AUC following single doses appeared proportional to dose (200-1200 mg).
- At 400 mg BID changes in 5-HIAA were comparable across studies. Mean change in plasma 5-HIAA was -52% from Day 1 to Day 14, (placebo +26%). Change in urine 5-HIAA was -52% (placebo +12%).
- Modeling of PK data predicts 400-600 mg RVT-1201 BID in humans will achieve the target exposure associated with efficacy in rat models.

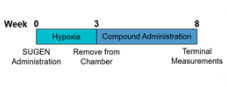
RVT-1201 was generally well tolerated in healthy subjects at doses required to achieve clinically-relevant AUC and lowering of serotonin biomarkers for treatment of PAH

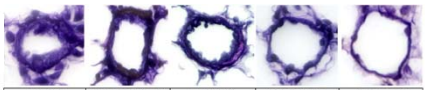
EFFICACY OF RVT-1201 IN RAT MODELS OF PAH

Oral RVT-1201 ameliorates PAH in the monocrotaline prevention model and the SUGEN-hypoxia treatment model of established PAH

- The median effective dose (100 mg/kg/day) was associated with reduced pulmonary vascular remodeling and ~50% reduction in urinary 5-HIAA reflecting total serotonin biosynthesis.
- RVT-1201 shows additive effects on vascular remodeling when administered with Ambrisentan.

RVT-1201 Decreases Pulmonary Vessel Wall Thickness in the SUGEN-Hypoxia Model





Treatment	Vehicle Control	Ambrisentan + Tadalafil	RVT-1201 200 mg/kg	RVT-1201 + Ambrisentan	Normoxic Control
Relative Vessel Wall Thickness	100%	78.4%	70.7%	58.6%	30.7%

Figure 1. PAH was induced by a single injection of Sutent® (SU5416, SUGEN) and exposure to hypoxia (11% O_2) for 21 days, followed by return to normoxia and indicated treatments once daily for an additional 28 days. Dose of RVT-1201 in combination studies was 100 mg/kg/day, Ambrisentan and Tadalafil were dosed at 10 mg/kg/day. Verhoeff-Van Gieson elastin staining (EVG) on Day 49 in cross sections of perfused, formalin fixed lungs. 40x magnification.

CLINICAL TOLERABILITY AND PHARMACOKINETICS

RVT-1201 was generally well-tolerated across both studies in ~120 healthy subjects

- No safety concerns identified following single doses ranging from 100 mg to 2000 mg or repeat 100 mg to 800 mg doses BID over 14 days.
- Treatment emergent adverse events resolved once study drug was discontinued, no serious adverse events (SAEs) or dose limiting toxicity were identified.

		KAR5585-101				RVT-1201-1001		
		Part 1: SAD		Part 2: MAD		Part 1: SAD	Part 2: MAD	
		Placebo	All doses	Placebo	All doses	All doses	Placebo	All doses
Total number of subjects	n	18	54	12	36	10	6	18
Age (years)	Mean (SD)	44.3 (12.6)	39.1 (11.9)	39.4 (11.1)	39.4 (12.8)	34 (12.2)	41.3 (11.6)	39.1 (10.9)
	Median	47.5	41.0	37.5	37	30.5	45.0	44.5
	Min, Max	24.0, 62.0	21.0, 63.0	20.0, 62.0	19.0, 64.0	20, 54	27, 52	22,54
Ethnicity	NOT HISPANIC OR LATINO, n (%)	17 (94.4)	52 (96.3)	12 (100)	29 (80.6)	10 (100)	6 (100)	18 (100)
	HISPANIC OR LATINO, n (%)	1 (5.6)	2 (3.7)	0	7 (19.4)	0	0	0
Sex	M, n (%)	10 (55.6)	28 (51.9)	5 (41.7)	18 (50.0)	10 (100)	6 (100)	17 (94.4)
	F, n (%)	8 (44.4)	26 (48.1)	7 (58.3)	18 (50.0)	0	0	1 (5.6)
BMI (kg/m²)	Mean (SD)	26.5 (3.9)	27.1 (4.0)	27.6 (3.5)	28.7 (3.1)	27.20 (3.87)	26.08 (2.97)	25.53 (3.49)
	Median	26.4	26.9	28.4	28.9	27.95	26.65	25.70
	Min, Max	20.4, 32.5	21.0, 34.8	21.2, 32.8	22.3, 33.6	19.4, 31.4	22.6, 29.6	19.3, 31.3

Table 1. Two single and multiple dose Phase 1 studies have been performed in healthy subjects

IR tablet formulation administered with food produces optimal pharmacokinetics

- Oral bioavailability of RVT-1201 and KAR5417 exposure increased and became less variable when RVT-1201 was administered as an immediate-release tablet with food compared to a dry-powder filled capsule given to fasted subjects.
- Steady-state exposures were achieved by 7 days of treatment.

Exposure to The Active Moiety KAR5417 is Greater and Less Variable When RVT-1201 is Administered as an IR Tablet With Food

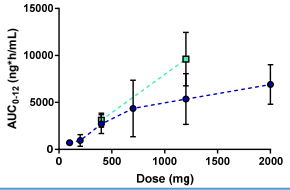


Figure 2. Arithmetic mean ± SD data for healthy subjects receiving RVT-1201 as either: a dry-filled capsule when fasted (KAR5585-101) or as multiple 100 mg immediate-release tablets (RVT-1201-1001) following a standard calorie meal.

SEROTONIN LOWERING IN HUMANS

In healthy individuals, RVT-1201 reduces serotonin biomarkers to levels consistent with those observed in preclinical studies

- Serotonin lowering in urine was measured using 5-HIAA/creatinine change from baseline (CFB). Reductions in urinary 5-HIAA with 800 mg BID (Study RVT-1201-1001) were comparable to the 400 mg BID regimen, with both doses affording a maximal reduction of ~60%, indicating that the higher dose did not result in additional reductions in serotonin biosynthesis.
- Plasma serotonin lowering was comparable across the two Phase 1 studies following a 400 mg BID 14-day regimen with a mean plasma 5-HIAA CFB of −52% from Day 1 to Day 14 compared to placebo (+26%).
- Net differences in plasma and urinary 5-HIAA were 78% and 64%, respectively.

RVT-1201 Lowers Serotonin Biosynthesis Following 7 and 14 Days of Treatment in Healthy Subjects

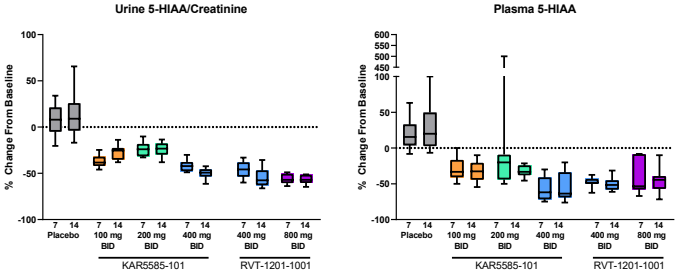


Figure 3. Percentage change from baseline of urine 5-HIAA: creatinine ratio and plasma 5-HIAA on Days 7 and 14 following twice daily repeat oral administration of RVT-1201 in studies KAR5585-101 and RVT-1201-1001. Whiskers, range; box, 25th-75th percentile and horizontal, median. Each treatment group represents data from 7 to 9 subjects. Data for subjects receiving placebo pooled across cohorts (n=15).

CLINICAL DOSE & SEROTONIN REDUCTION FOR PAH

- A ~50% reduction in 5-HIAA was achieved on Day 7 in 2 of 8 (25%) of subjects receiving 400 mg BID RVT-1201 with the frequency increasing to 6 of 8 (75%) by Day 14. At 800 mg BID, 6 of 7 (86%) and 7 of 7 (100%) subjects achieved ~50% reduction in 5-HIAA on Days 7 and 14, respectively.

RVT-1201 Administration Achieves ~50% Serotonin Reduction by Day 14 of Treatment

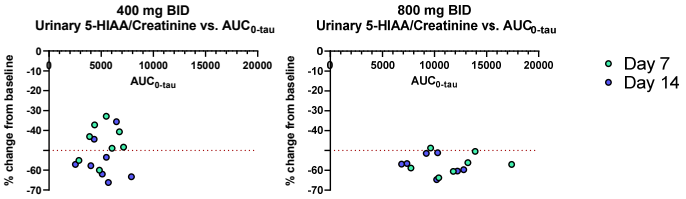


Figure 4. Data for healthy subjects receiving RVT-1201 as multiple 100 mg immediate release tablets (RVT-1201-1001) following a standard calorie meal.

- Combining data from both regimens, KAR5417 Day 14 $AUC_{0\text{-}tau}$ values ≥2530 ng.hr/mL were associated with >50% reductions in urinary 5-HIAA in 87% (13/15) of subjects.
- 400-600 mg BID is predicted from the Phase 1 data as the human equivalent dose required to exceed the target AUC associated with achieving ~50% reduction in serotonin biosynthesis by Day 14.

600 mg BID oral RVT-1201 was selected to achieve an AUC associated with at least 50% lowering of serotonin biosynthesis

- The 600 mg BID regimen should be generally well-tolerated as the higher 800 mg BID regimen was in RVT-1201-1001.

Predicted KAR5417 Exposures for the 600 mg BID Dosing Group

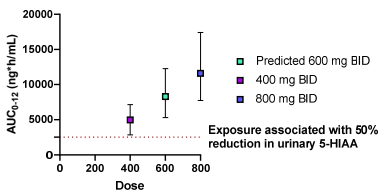


Figure 5. Predicted geometric mean ± range for the 600 mg BID dose. Expected values for the 600 mg BID dose was predicted by interpolation of data from the 400 mg BID and 800 mg BID exposure during steady state (Day 7).

CONCLUSIONS

- A target for lowering of serotonin biosynthesis (~50% reduction in urinary 5-HIAA) that is associated with nonclinical efficacy provides a basis for RVT-1201 clinical dose selection.
- In healthy subjects, oral RVT-1201 achieved target reduction in serotonin by 14 days.
- 400-600 mg BID oral RVT-1201 is predicted as the human dose required to exceed the AUC associated with ~50% reduction in serotonin biosynthesis.
- A 600 mg BID regimen should be generally well-tolerated as the higher 800 mg BID regimen was in RVT-1201-1001.
- In summary, RVT-1201 was generally well tolerated in healthy subjects at doses that exceed the AUC associated with lowering of serotonin biomarkers for treatment of PAH.