In Vitro Pharmacology and Preclinical Efficacy of IKT-001 in Pulmonary Arterial Hypertension

POSTER NUMBER: 9137

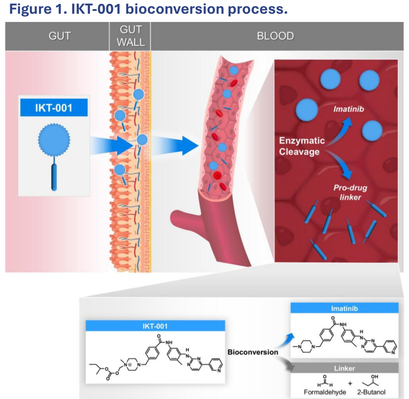
J.W. Adams[1], I. Gaidarov[2], M.D. Zammit[3], M.R. Gralinski[3], K.R. Doherty[3], C. Cabell[1]

[1]Inhibikase Therapeutics, Inc., Wilmington, DE, US; [2]Eurofins Beacon Discovery, San Diego, CA, US; [3]CorDynamics, Inc., Chicago, IL, US

Background

- Aberrant signaling through PDGFRα, PDGFRβ, and c-Kit tyrosine kinases drives cellular proliferation/migration and plays a key role in PAH pathophysiology.[1,2]
- Imatinib, a potent inhibitor of PDGFRα, PDGFRβ, and c-Kit, has shown efficacy in PAH patients.[3,4] However, tolerability issues, including GI side effects, resulted in significant drug discontinuation in PAH trials, impeding further development.[2-4]
  - c-Kit activity in gut sub-mucosa is known to regulate gut contractility and motility.[5,6]
  - Impairment of intestinal contractility by imatinib in rodents is thought to be mediated by c-Kit pathway inhibition.[7,8]
- IKT-001, a novel, investigational prodrug of imatinib, was designed to minimize direct GI exposure to imatinib and reduce GI-related side effects.
  - IKT-001 is stable in representative gut fluids.[9]
  - Once entering the blood, IKT-001 is cleaved rapidly to generate free circulating imatinib (**Figure 1**). In vitro studies have demonstrated that the plasma half-life of IKT-001 is <5 minutes in human plasma.[9] In vivo studies in rats have shown that IKT-001 is undetectable in portal and systemic circulation within 10 minutes of oral dosing.[9]

Figure 1. IKT-001 bioconversion process.



Objectives

- Assess in vitro pharmacologic activity of IKT-001 and imatinib at key tyrosine kinases associated with PAH efficacy and tolerability.
- Compare the in vivo and ex vivo effects of IKT-001 and imatinib in mouse models of GI motility.
- Evaluate the in vivo efficacy of IKT-001 in a standard rodent model of PAH.

Methods

In vitro biochemical and cell-based assays

- Biochemical assay: Promega ADP-Glo assay technology was used to measure IKT-001 and imatinib activities at purified PDGFRα, PDGFRβ, and c-Kit enzymes.
- Cell-based assay: Primary cells and cell lines were obtained commercially and utilized for enzyme-linked immunosorbent- or homogeneous, time-resolved fluorescence-based assays measuring phosphorylation of receptor-tyrosine kinases and/or their substrates Erk1/2 phosphorylation.

Ex vivo and in vivo mouse models of GI motility

- Effects of drugs on spontaneous contractile activity was measured ex vivo in intestinal rings removed from male BalbC mice.
  - Vehicle, imatinib (30 μM), and IKT-001 (30 μM) were evaluated in isolated rings using a crossover experimental design.
- The effects of vehicle, imatinib (50 and 100 mg/kg), and IKT-001 (50, 100, and 150 mg/kg) were analyzed in vivo in male BalbC mice for effects on gastric motility using charcoal propulsion assay. Both were administered orally 60 minutes before charcoal.

In vivo rodent model of PAH

- In vivo efficacy was assessed using single-dose SU5416 plus low oxygen for 22 days to induce PAH in rats.
- Rats were treated with imatinib (100 mg/kg) or IKT-001 (100 or 150 mg/kg) starting on Day 22 under normoxic conditions until Day 43 terminal procedures.
- Echocardiography, performed on Day 21 in a select group and Day 42 in all other groups, hemodynamics, heart/lung measurements, and pulmonary vascular histology were performed on Day 22 (pretreatment disease baseline in a select group) and Day 43 (end of treatment in all remaining groups).

Results

In vitro results

- In vitro findings indicate that IKT-001 has less inhibitory activity at PDGFRα/β and c-Kit in both biochemical and cell-based assays compared with imatinib (**Table 1**).

Table 1. In vitro pharmacology of imatinib and IKT-001: inhibition of tyrosine kinase activity.

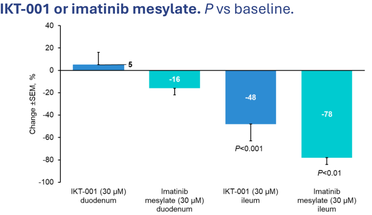
	Biochemical assay (Mean IC_{50}, nM)		Cell-based assay (Mean IC_{50}, nM)	
Kinase	Imatinib	IKT-001	Imatinib	IKT-001
PDGFRα	1.1	9.7	291.7	4715.2
PDGFRβ	9.6	133.0	1708.0	>100,000
c-Kit	40.8	164.6	539.5	9982.7

Results (cont'd)

Ex vivo and in vivo mouse models of GI motility

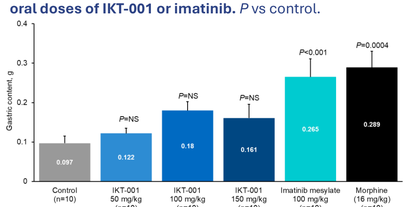
- Imatinib mesylate (30 μM) slightly decreased the amplitude of spontaneous contractions of the duodenum whereas IKT-001 (30 μM) had no effect. Both imatinib mesylate and IKT-001 significantly decreased the amplitude of spontaneous contractions of the ileum vs baseline (P<0.01 and P<0.001, respectively); however, the effects were less pronounced with IKT-001 than with imatinib mesylate (**Figure 2**).

Figure 2. Mean (±SEM) percent change from baseline of spontaneous duodenal and ileal contractions following IKT-001 or imatinib mesylate. P vs baseline.



- IKT-001 had no significant effects on gastric content weight (gastric emptying) compared with control, although a trend towards an increase was observed across doses (+26% for 50 mg/kg, +86% for 100 mg/kg, and +66% for 150 mg/kg; P=NS). Conversely, similar to the positive control morphine, imatinib 100 mg/kg significantly increased gastric content weight vs control (+173%; P<0.001) (**Figure 3**).

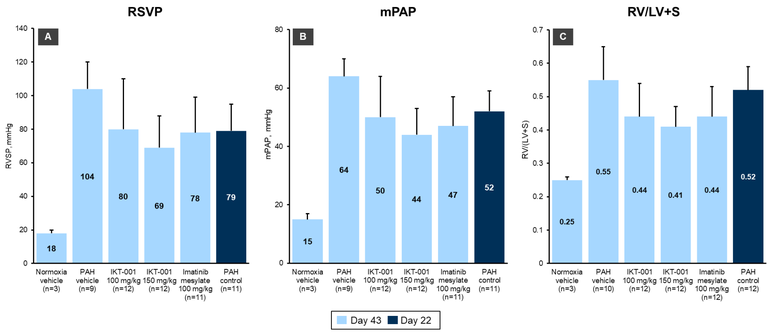
Figure 3. Mean (±SEM) gastric content following single oral doses of IKT-001 or imatinib. P vs control.



Rodent model of PAH

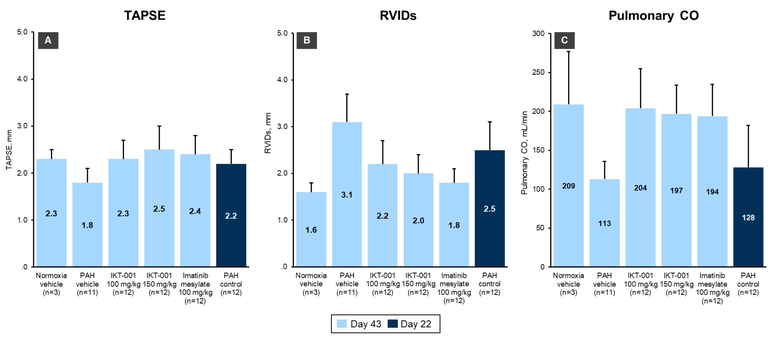
- In the rat PAH model, treatment with IKT-001 100 mg/kg or 150 mg/kg after disease onset attenuated PAH, as demonstrated by improvements in RVSP and mPAP, with efficacy similar to that observed for imatinib mesylate 100 mg/kg (**Figure 4**).
- PAH resulted in substantive increases in RV weight, as indicated by an increase in Fulton's Index (RV/LV+S). As shown in **Figure 4**, treatment with IKT-001 or imatinib attenuated right heart hypertrophy.
- Notably, IKT-001 150 mg/kg tended to reverse PAH endpoints resulting in hemodynamic and structural improvements compared with treatment initiation with a statistically significant improvement in Fulton's Index observed at Day 43 vs Day 22 (P<0.05).

Figure 4. Mean (±SD) RSVP (A), mPAP (B), and RV/LV+S (C) at Day 43 in normoxia vehicle, PAH vehicle, and rats treated with IKT-001 or imatinib, and at Day 22 in PAH control rats.



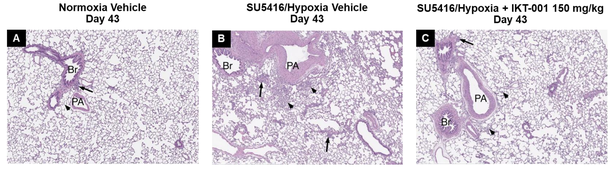
- As shown in **Figure 5**, animals treated with IKT-001 100 mg/kg or 150 mg/kg exhibited improvements in RV morphologic changes, RV function, and pulmonary flow, with efficacy similar to what was seen with imatinib 100 mg/kg.

Figure 5. Echocardiographic assessments of TAPSE (A), RVIDs (B), and pulmonary CO (C) at Day 43 in normoxia vehicle, PAH vehicle, and rats treated with IKT-001 or imatinib, and at Day 22 in PAH control rats. Data are mean (±SD).



- Lung histopathology findings were typical of PAH, including pulmonary artery remodeling. IKT-001 was associated with lowered histopathology lesion severity including decreased pulmonary artery intimal hypertrophy (**Figure 6**).

Figure 6. Representative photomicrographs of H&E histopathology from normoxia vehicle (A), SU5416/hypoxia vehicle (B), and SU5416/hypoxia + IKT-001 150 mg/kg (C). Examples of pulmonary artery (PA) and bronchiole (Br) are indicated in each image.



Conclusions

- In vivo results confirm imatinib-like efficacy of IKT-001 in a PAH rat model, including reversal of key PAH disease markers.
- Compared with imatinib, IKT-001 has less inhibitory activity at tyrosine kinases including PDGFRα/β and c-Kit supporting its potential to reduce direct exposure of imatinib to the GI tract.
- Ex vivo and in vivo analyses demonstrate less impairment of GI motility for IKT-001 compared to imatinib suggesting potential for improved GI tolerability.

References

1. Mouratoglou SA, et al. *Int J Cardiol Congenit Heart Dis*. 2025;21:100594.
2. Pullamsetti SS, et al. *Int J Mol Sci*. 2023;24:12653.
3. Ghofrani HA, et al. *Am J Respir Crit Care Med*. 2010;182:1171-1177.
4. Hoeper MM, et al. *Circulation*. 2013;127:1128-1138.
5. Sanders KM, et al. *J Physiol*. 2023:10.113/JP284745.
6. Rømert P, Mikkelsen HB. *Histochem Cell Biol*. 1998;109:195-202.
7. Shimojima N, et al. *Pharmacology*. 2005;74:95-99.
8. Hashitani H, et al. *Br J Pharmacol*. 2008;154:451-459.
9. Adams JA, et al. Poster 8948. Presented at ATS 2026 International Conference; May 15-20, 2026: Orlando, Florida.

Corresponding Author: John Adams, jadams@inhibikase.com

Abbreviations

CO, cardiac output; GI, gastrointestinal; H&E, hemotoxylin and eosin; IC_{50}, half maximal inhibitory concentration; LV, left ventricle/ventricular; PDGFR, platelet-derived growth factor receptor; mPAP, mean pulmonary artery pressure; NS, not significant; PAH, pulmonary arterial hypertension; RV, right ventricle/ventricular; RVIDs, right ventricle internal diameter during systole; RVSP, right ventricular systolic pressure; S, septum; SEM, standard error of the mean; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

ATS 2026 International Congress
15–20 May 2026 • Orlando, Florida