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The Influence of Route of Delivery and Formulation on the Pulmonary Pharmacokinetics of Imatinib in Nonclinical Species

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INTRODUCTION

- Imatinib, a tyrosine kinase inhibitor, has demonstrated clinical improvements in pulmonary arterial hypertension (PAH) in human trials when administered orally in addition to standard of care[1-3]
- However, significant adverse events occurred and the development of oral imatinib for the treatment of PAH was discontinued[1]
- Inhaled drug delivery is an alternative means of targeting the disease, with the potential to reduce the therapeutic dose and minimize side effects

OBJECTIVE

- To demonstrate lung and plasma pharmacokinetics of imatinib and N-desmethyl imatinib in mice, rats, and cynomolgus monkeys following delivery of solutions, suspensions, and dry powders of imatinib to the lungs and compare with observed data following oral dosing

METHODS

- Imatinib was administered by nasal aspiration to C57BL6/J mice, and Sprague Dawley rats received formulations via intratracheal (IT) instillation in solution, suspension, or dry powder insufflation
  - Serial blood samples were periodically drawn from animals over 24 hours while lung tissue homogenates were obtained through terminal sampling per time point in separate evaluations
- For aerosol studies, Sprague Dawley rats inhaled dry powder for 1 hour daily via nasal exposure only, while cynomolgus monkeys were exposed to dry powder aerosols via face mask for 30 minutes daily for 28 days
  - Toxicokinetic evaluations were carried out on Days 1 and 28 for both species
- Blood samples were processed, and plasma was analyzed for imatinib and the principal metabolite, N-desmethyl imatinib, using bespoke liquid chromatography-mass spectrometry (LC-MS) procedures
- Noncompartmental pharmacokinetic assessments were performed using WinNonlin® software (Certara, Inc., Princeton, NJ)

RESULTS

Pharmacokinetics of IT Administration

- Imatinib lung tissue exposures were substantially higher following pulmonary delivery to mice (data not shown) and rats (**Table 1**) via intranasal or IT administration compared to oral or intravenous administration
- Formulation impacted the extent of lung retention with the following progression: dry powder > suspension > solution > oral ≥ intravenous delivery in rats
- Lung area under the curve (AUC) values following IT dry powder delivery in rats were >70-fold higher than oral delivery while plasma AUC values were within 4-fold, suggesting preferential lung retention via direct lung dosing

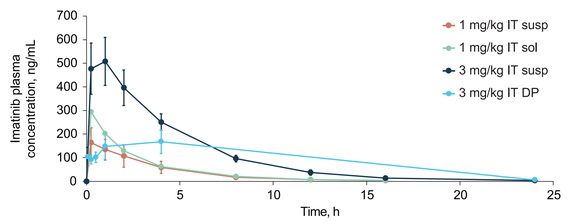
Table 1. Pharmacokinetic Parameters and Lung to Plasma Ratios in Rats

	PO[a]		IV		IT sol		IT susp				IT DP[a]	
	3 mg/kg		1 mg/kg		1 mg/kg		1 mg/kg		3 mg/kg		3 mg/kg	
	Lung	Plasma	Lung	Plasma	Lung	Plasma	Lung	Plasma	Lung	Plasma	Lung	Plasma
C_{max}, ng/mL (CV %)	1180 ± 832 (71)	74.8 ± 46.1 (62)	2125 ± 608 (29)	467 ± 18.2 (4)	19,225 ± 3759 (20)	294 ± 27.9 (9)	41,875 ± 7690 (18)	164 ± 31.6 (19)	151,000 ± 14,832 (10)	512 ± 51.3 (10)	97,100 ± 25,885 (27)	168 ± 49.7 (30)
T_{max}, h	4	4	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.81	0.083	4
MRT, h	5.9	4.7	NC	2.8	NC	2.9	NC	2.3	NC	4.4	5.2	6.7
AUC_{last}, ng·h/mL (CV %)	6660	404	7675	1042 ± 31.4 (3)	20,641	822 ± 56.7 (7)	70,375	636 ± 136 (21)	345,066	2645 ± 182 (7)	469,000	1570
Plasma F, %	–	13	–	N/A	–	79	–	61	–	85	–	50
Kp, $\frac{lung}{plasma}$	17		7.4		25		111		129		299	

AUC_{last}, area under the curve from time 0 to the last measurable concentration; C_{max}, maximum concentration; CV, coefficient of variation; F, bioavailability; IT DP, intratracheal dry powder; IT sol, intratracheal solution; IT susp, intratracheal suspension; IV, intravenous; Kp, lung/plasma partitioning ratio; MRT, mean residence time; N/A, not available; NC, not calculated; PO, oral administration; T_{max}, time to reach maximum concentration.
[a]Dry powder and oral results were obtained from a separate study from the results shown for the IV, IT sol, and IT susp evaluations but are combined here for clarity.

- Initial stable or rising plasma concentrations observed with suspension doses in rats are also indicative of dissolution rate-limited absorption in contrast to the rapid decline in plasma concentration immediately after solution-based dosing (**Figure 1**)

Figure 1. Imatinib Plasma Concentration Over Time in Rats Following IT Administration[a]

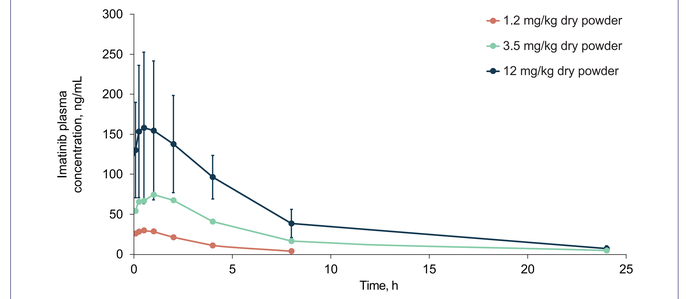


IT, intratracheal; IT DP, intratracheal dry powder; IT sol, intratracheal solution; IT susp, intratracheal suspension.
[a]n ≥3 per group.

Pharmacokinetics of Aerosol Administration

- Repeat dose (28-day) dry powder aerosol inhalation to rats (5-17 mg/kg/day) and cynomolgus monkeys (1.2-12 mg/kg/day) suggested high lung partitioning, as evidenced at the 24-hour time point
  - Lung/plasma partitioning ratios in rats ranged from 18 to 25 for dry powder aerosol inhalation versus 4.9 for oral administration (20 mg/kg/day) and from 135 to 705 for dry powder aerosol inhalation in monkeys, depending on the achieved dose
- Plasma time course data in the primates also exhibited profiles suggestive of dissolution rate–limited absorption, although a contribution via oral uptake cannot be ruled out (**Figure 2**)

Figure 2. Imatinib Plasma Concentrations Over Time in Cynomolgus Monkeys Following Aerosol Administration of Dry Powder[a]



[a]n = 6 for each target dose.

Imatinib Metabolism

- There was no apparent contribution to metabolism arising from the lungs, as assessed by the relative quantities of the N-desmethyl imatinib metabolite to imatinib in lung tissue versus plasma (**Table 2**)

Table 2. N-desmethyl Metabolite CGP74588 in Mice and Rats Following PO, IT, and IN Delivery of 3 mg/kg Imatinib

	Mouse						Rat					
	Lung			Plasma			Lung			Plasma		
	PO	IT susp	IN	PO	IT susp	IN	PO	IT susp	IT DP	PO	IT susp	IT DP
Imatinib AUC_{last}, ng·h/mL	2600	13,000	22,000	486	499	660	6660	61,700	459,000	404	1110	1570
Metabolite AUC_{last}, ng·h/mL	51.8	161	336	45.5	23.3	31	992	3890	1780	16.8	47.7	ND
Metabolite relative to imatinib, %	2	1.2	1.5	9.3	4.7	4.7	15	6.3	0.4	4.2	4.3	<1

AUC_{last}, area under the curve from time 0 to the last measurable concentration; IN, intranasal; IT, intratracheal; IT DP, intratracheal dry powder; IT susp, intratracheal suspension; ND, not detected; PO, oral administration.

Key Messages

- The inhaled route of administration demonstrated higher lung tissue to plasma ratios than oral administration
- Formulation effects can be significant, with inhaled dry powder exhibiting "improved" pharmacokinetics versus a solution formulation

Conclusions

- Observations in nonclinical species demonstrated that pulmonary delivery of imatinib can achieve substantial lung exposure and potentially enhance the response to the widespread pulmonary vasculopathy observed in PAH
- Inhaled delivery of a dry powder imatinib has the potential to achieve therapeutic benefit at a lower dose than with oral administration and concomitantly may exhibit a reduction in adverse events

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DISCLOSURES

Ralph Niven, Hunter Gillies, and Benjamin Dake are employees of Aerovate Therapeutics, Inc. Anne Cooper, AEC Scientific Consulting. Ron K. Wolff is an employee of RK Wolff Safety Consulting, Inc.

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