Dry powder inhaled ribavirin in healthy volunteers: safety, tolerability, lung and systemic pharmacokinetics

Poster No. 2206

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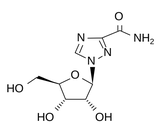
Introduction

Dry Powder Ribavirin for Inhalation

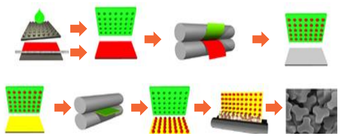
- Ribavirin (**Figure 1a**) is approved for clinical use:
  - as a nebulized solution to treat infant respiratory syncytial virus (RSV) at a dose of 6 g/day for 3–7 days
  - as part of an oral combination treatment for hepatitis C virus (HCV), at a dose of 800–1400 mg/day for up to 48 weeks
- Particle Replication in Non-wetting Templates (PRINT) (**Figure 1b**)
  - For more information visit http://liquidia.com/print-technology/
  - Inhalation pharmacokinetic (PK) studies showed PRINT particles improved delivery to rat lungs by 25-fold compared with micronized lactose blend or spray-dried-dispersion
  - The formulation of PRINT particles used in this study: ribavirin:trehalose:trileucine 35:55:10, amorphous powder

Figure 1a. Ribavirin is a broad-spectrum antiviral agent | **Figure 1b. PRINT particles (Liquidia Technologies)**

1a.



1b.



Proposed Ribavirin Treatment Paradigm in Chronic Obstructive Pulmonary Disease (COPD)

- Head colds in patients with COPD can lead to disease exacerbation[1,2] and resulting decline in lung function[3,4]
- Respiratory viruses have been detected in 22–64% of COPD exacerbations[1]
- Exacerbations are believed to be triggered when the virus migrates from the upper airway into the lower lung
- Ribavirin has modest broad-spectrum activity against key respiratory viruses, with EC_{50} versus human rhinoviruses (HRV), RSV and influenza virus (IFV) of 150 µM, 12 µM and 12 µM, respectively
- Hypothesis: Prevention of virus migration from the upper to lower lung by treating patients with COPD at the onset of a head cold will prevent exacerbation

What Level of Ribavirin do we Need?

High Levels in the Lung for Efficacy

- The goal is to prevent migration of virus, not to treat a full viral infection
- Ribavirin pharmacodynamics are assumed to be C_{max} driven; therefore our target was to exceed C_{max} of 200 µM in epithelial lining fluid (ELF) to cover the EC_{50} of 150 µM against HRV
- Using inhaled ribavirin physiology-based PK model, a **30 mg BID dose** was predicted to achieve a C_{max} of approximately 800 µM

Low Level in the Systemic Circulation for Safety

- Genotoxicity[5], but not carcinogenicity, observed in animals
- Teratogenicity
  - Exclude women of childbearing potential and use appropriate contraception for partners of male participants
  - Administer drug to subjects in a negative pressure enclosure to minimize risk of exposure to clinical staff

Aims

Primary

- To investigate the safety and tolerability of inhaled dry powder ribavirin following single escalating doses in healthy subjects
- To investigate systemic PK of inhaled dry powder ribavirin following single escalating doses in healthy subjects
- To investigate lung concentration of ribavirin following single escalating doses of inhaled dry powder ribavirin in healthy subjects

Other aims

- To investigate the safety and tolerability of inhaled dry powder placebo following single escalating doses in healthy subjects
- To assess dose proportionality of inhaled dry powder ribavirin compared with systemic PK parameters

Methods

- Healthy male and female subjects aged 18–65 years were recruited
- Subjects were randomly assigned to receive either ribavirin or matching placebo particles
- Subjects inhaled ribavirin or placebo inside a negative pressure tent
- Subjects were monitored closely on-site for 24 hours after dosing
  - Safety and tolerability were assessed, including assessment of lung function by spirometry
- Blood was collected before and at multiple points after dosing to obtain systemic PK parameters
- In selected cohorts:
  - Lung concentration of ribavirin was assessed by bronchoalveolar lavage (BAL)
  - ELF and lining cells were collected by four passes of lavage fluid; the first pass was discarded and the last

Study Design

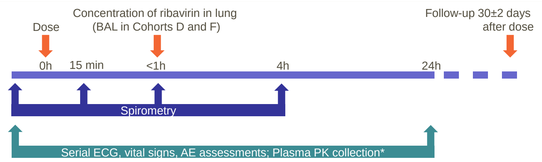
- A single ascending dose of ribavirin was administered in healthy subjects (**Table 1 and Figure 2**)

Table 1. Summary of study cohorts and dosing

Cohort	N Active/PB	Dose* (mg)
A	6/2	7.5
B	6/2	15
C	6/2	30
D (with BAL)	12/2	30
Comprehensive Review of safety and systemic and BAL PK		
E	6/2	60
F (with BAL)	12/2	60

BAL, bronchoalveolar lavage; N, number of subjects; PB, placebo; PK, pharmacokinetics
*administered as capsules each containing 7.5 mg active ingredient

Figure 2. Study design



AE, adverse event; BAL, bronchoalveolar lavage; ECG, electrocardiogram; h, hour; PK, pharmacokinetic
*Plasma PK collection also took place at 48h and 72h after dosing in Cohorts C and E.

Results

Subjects

- In total, 60 healthy subjects were enrolled, 48 of whom received ribavirin; subject characteristics are summarized in **Table 2**.

Table 2. Subject characteristics

Characteristic	Healthy Subjects N=60
Age, years [mean (SD)]	36.8 (12.31)
Sex [n (%)]	
Female	6 (10)
Male	54 (90)
BMI, kg/m² [mean (SD)]	25.26 (2.537)
Ethnicity [n (%)]	
Hispanic or Latino:	1 (2)
Not Hispanic or Latino:	59 (98)
Race [n (%)]	
Asian	8 (13)
Black or African American	9 (15)
White/Caucasian/European Heritage	39 (65)
Multiple or not collected	4 (2)

BMI, body mass index; n, number; SD, standard deviation

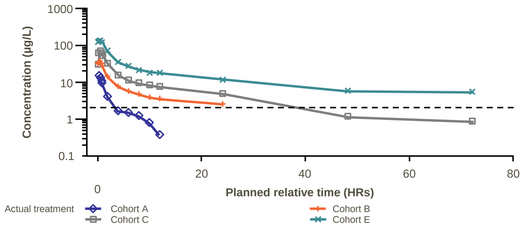
Safety and Tolerability

- There were no deaths or serious adverse events (SAEs) reported in the study
- Of the 60 subjects in the study, 25 reported adverse events (AEs) and 12 reported possibly drug-related AEs
  - The most common AEs were headache and cough, occurring in 11 and 3 subjects, respectively
- All AEs were of mild or moderate intensity with no apparent dose response
- No clinically significant trend was observed in the laboratory, echocardiogram (ECG), telemetry, spirometry, or vital signs assessments
- There were no device performance issues observed in the study

Plasma PK Profiles

- Ribavirin was quantifiable in plasma in all subject cohorts immediately (within 15 mins) after inhalation, indicating rapid absorption from the lungs (**Figure 3**)
- C_{max} increased proportionally from 7.5 mg to 60 mg. AUC_{inf} was dose proportional from 15 mg to 60 mg (**Table 3**)
- Due to the small sample size for each treatment cohort and the limited sampling times, the estimation of half-life ($t_{½}$), AUC_{inf} and dose proportionality should be interpreted with caution

Figure 3. Ribavirin plasma concentration by dose over time (semi-logarithmic scale)



Results

Table 3. Ribavirin PK parameters by dose

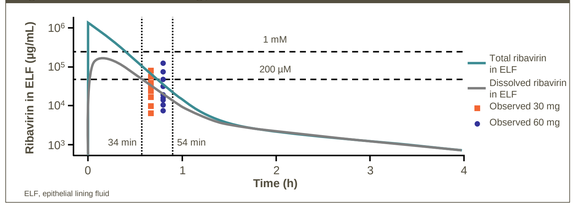
Dose, mg	C_{max}, ng/mL	$t_{1/2}$, h	AUC_{inf}, h*ng/mL
7.5	13.6	5.9	36.6
15	37.7	19.7	206.0
30	65.0	25.1	421.4
60	140.0	25.4	1062.1

AUC_{inf}, area under the curve from time zero to infinity; C_{max}, maximum serum concentration; $t_{1/2}$, apparent half-life

Ribavirin Lung Concentration

- **HYPOTHESIS**: We need to achieve a minimum C_{max} of 200 µM in ELF
- **RESULT**: Concentrations of ribavirin in the ELF of 101 µM (dose, 30 mg) and 112 µM (dose, 60 mg); these concentrations correspond to C_{max} >300 µM (**Figure 4**)

Figure 4. Predicted (30 mg) and observed ribavirin concentration in the ELF



ELF, epithelial lining fluid

Conclusions

- The size and uniformity of the Liquidia particles allowed efficient delivery of ribavirin to the lung (assessed by levels in ELF)
- Target lung C_{max} (>200 µM) was achieved with single doses of 30 mg and 60 mg in healthy subjects
- There were no deaths or SAEs reported in the study
- All AEs were of mild or moderate intensity with no apparent dose response
- There were no device performance issues observed in the study
- No clinically significant trend was observed in the laboratory, ECG, telemetry, spirometry, or vital signs assessments
- Following inhalation, ribavirin appeared quickly in the plasma, and there was approximately proportional increase in C_{max} with increase in dose

Acknowledgements, Funding and Disclosures

- The authors thank all volunteers who took part in this study and the staff of Hammersmith Medicines Research for performing this study.
- Liquidia for development and manufacturing of PRINT formulation ribavirin.
- This study (202031) was funded by GlaxoSmithKline.
- Editorial assistance was provided by Katy Tucker at Fishawack Communications UK, Ltd; this service was supported by GlaxoSmithKline.
- Julia Billiard, Steve Baker, Vijayalakshmi Chandrasekaran, Shuying Yang, Etienne Dumont are employees and stockholders in GSK . Frans van den Berg is an employee of Hammersmith Medicines Research (Contract Research Organisation)

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Presented at the ERS International Congress, Milan, Italy, 9–13 September 2017

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