

Multiple-dose safety and pharmacokinetics of A-60444, a novel compound active against Respiratory Syncytial Virus (RSV)

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ABSTRACT

Background

A-60444 is a novel and potent inhibitor of RSV replication. The objectives of this Phase I study were to determine the safety, tolerability and pharmacokinetics (PK) of multiple doses of A-60444, and to establish the relationship between exposure and *in-vitro* anti-viral activity.

Methods

24 healthy males were enrolled into this double-blind, placebo-controlled, dose-escalation study. 8 subjects in each of 3 dose cohorts were randomised to receive 7 daily oral doses of A-60444 (6 subjects) or placebo (2 subjects). A high-fat breakfast was given 30min before each dose. Cohort 1: 150mg; cohort 2: 300mg; cohort 3: 600mg Day 1 followed by 450mg Days 2-7. Safety was assessed via adverse events, vital signs, 12-lead ECG, twin channel ECG telemetry, haematology, biochemistry and urinalysis. Plasma and urine A-60444 were measured by HPLC-MS/MS; PK parameters calculated by SAS v 8.2.

Results

A-60444 was well-tolerated in all dosing regimens. No serious adverse events were reported. There were no clinically significant changes in vital signs, ECG or twin channel ECG telemetry. There were 23, 13 and 6 adverse events reported from the 150, 300 and 600/450mg regimens respectively; all events resolved. Plasma concentrations of A-60444 above the *in vitro* IC₉₀ values were achieved in all 3 dosing regimens. Subjects given a loading dose of 600mg A-60444 followed by 6 days of 450mg achieved trough concentrations above the *in vitro* IC₉₀ at the end of Day 1 and were $\geq 4 \times$ IC₅₀ and $\geq 2 \times$ IC₉₀ for the following 6 days.

Conclusions

7 day oral dosing of A-60444 from 150 to 600/450mg was well-tolerated with no clinically significant effects. Plasma concentrations in excess of *in vitro* IC₅₀ and IC₉₀ values were obtained with the regimen of 600mg followed by 450mg, suggesting A-60444 will be a well-tolerated and effective oral compound for the treatment of RSV infection.

INTRODUCTION

A-60444 is a highly potent inhibitor of RSV replication. It shows potent sub-micromolar activity in plaque assay against RSV with IC₅₀ values of 0.7-0.9 μ M, approximately 30-times more active than ribavirin.

The Phase I single oral dose study showed that doses of A-60444 from 25 to 600mg once daily were well-tolerated, with no observed clinically significant effects. Dosing after a high fat meal significantly improved bioavailability and the half-life suggested once daily dosing.

The objectives of this study were to determine the safety, tolerability and pharmacokinetic profile of 7 days dosing of A-60444 in healthy, young male subjects.

METHODS

Three parallel, double blind dosage groups of 8 healthy male subjects (Groups 1, 2 and 3) each received three different oral dosage regimens of A-60444 or placebo for 7 days. Subjects were Caucasian males between 18 and 55 years of age and were in good health as determined by a medical history, medical examination, electrocardiograph, serum biochemistry, haematology, urinalysis, and serology (Hepatitis, B, C and HIV).

A-60444 or matching placebo was administered as an oral syrup suspension 30 minutes after completion of a high-fat meal (FDA breakfast consisting of approximately 800-1000 calories, 50% from fat). Subjects in groups 1 and 2 were dosed on the morning of Day 1, had 1 day washout and then were dosed for 7 days continuously. Subjects in group 3 received 7 days dosing.

Adverse events were monitored continuously during the study. Laboratory safety tests (haematology/biochemistry & urinalysis) were conducted regularly, as were vital signs (temperature, blood pressure, heart rate). Twin channel telemetry monitoring was performed 12 hours before each dose and to 8 hours after each dose and 12 lead ECGs were measured at screening, and on the first and last days of treatment.

Samples for full plasma and urine PK profiles were taken on Day 1 and the last day of the multiple dosing.

RESULTS

Pharmacokinetics: Oral A-60444 given after a high-fat meal was absorbed from the gastrointestinal tract (GIT) and exhibited dose dependent pharmacokinetics with bi-exponential elimination

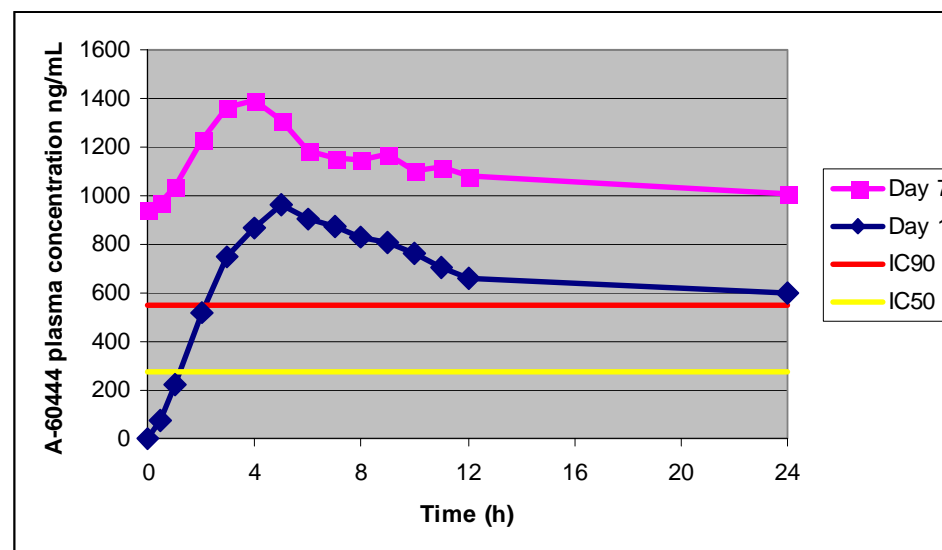
$t_{1/2}$ was long, ranging from 30-76h indicating suitability for once daily administration in the presence of normal physiological clearance mechanisms.

Over 7 days dosing, there was a moderate increase in A-60444 exposure and a small decrease in $t_{1/2}$ indicating time dependent elimination due either to drug metabolism auto-induction or increase in renal clearance or a combination of both.

Table 1: Mean Pharmacokinetic parameters of A-60444 following multiple days dosing

Dose (mg)	Regimen	C _{max} (mg/mL)	t _{max}	t _{1/2}	AUC ₀₋₂₄ (ng.h/mL)
150	Day 1	398	4.5	48	5819
	Day 9	651	4.7	37	11741
300	Day 1	611	4.3	76	8678
	Day 9	1028	3.6	30	17519
600	Day 1	1013	4.8	55	14781
	450 Days 2-7	1421	4.0	39	26717

Graph 1: Mean plasma concentrations on Day 1 and Day 7 of A-60444 during 600/450mg regimen



Safety: A-60444 was well tolerated in healthy males in doses up to 600mg on Day 1 followed by 450mg on Days 2-7.

No subjects were withdrawn from the study due to safety or tolerability concerns.

There were no serious or severe adverse events. The vast majority of adverse events were not considered drug-related.

There was no trend of an increase in either adverse events or adverse drug reactions as doses and exposures escalated.

Only 4 subjects had 6 adverse events reported as possibly drug-related, these were mild increases in liver enzymes, which were all asymptomatic and resolved spontaneously. These are thought likely to be due to the incarceration effect reported from Phase I units.

There were no clinically significant changes in vital signs, ECGs or telemetry readings at any of the dose levels studied.

Table 2: Non serious adverse events:

Dose (mg) OD	AE (n)	Pre-Dose	Mild	Mod	Severe	Drug-related	Resolved
150	23	2	18	5	0	3 possible	Y
300	13	0	11	2	0	1 possible	Y
600/450	9	0	8	1	0	2 possible	Y

CONCLUSIONS

This study set out to evaluate the safety, tolerability and pharmacokinetics of A-60444 in healthy human subjects. In healthy males A-60444 was safe and well tolerated at the dose regimens studied with no serious adverse events and no indications of any potential drug related side effects.

Orally administered A-60444 was absorbed from the gastrointestinal tract and exhibited dose dependant pharmacokinetics with bi-exponential elimination.

A loading dose of 600mg on Day 1 followed by 450mg on Days 2-7 provided plasma concentrations more than twice the *in vitro* IC₉₀ suggesting A-60444 will be a well-tolerated and effective oral compound for the treatment of RSV infection.