Flexible Single Day Ascending Dose (SDAD) Studies with AZD5847 Demonstrate Oral Dosing Regimens with Potential Utility for the Treatment of Tuberculosis (TB)

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Abstract

Background: AZD5847 (previously referred as AZD2563 in Gravestock MB *et al*. Bioorg Med Chem Lett 2003;13:4179–86) is an oxazolidinone antibiotic demonstrating activity versus *Mycobacterium tuberculosis* in acute and chronic murine models. $AUC_{0\text{-}24}$/MIC is the primary variable linked to efficacy. These intravenous (iv) and oral SDAD studies suggest oral dosing strategies that may be useful for the treatment of TB.

Method: Two different double-blind, placebo-controlled studies were performed in healthy volunteers with iv disodium phosphate prodrug and oral AZD5847. Sequential cohorts received single iv doses (1/2 hour infusion) of 60, 200, or 600 mg. In a second study, sequential oral doses of 50, 200, 600 and 1200 mg once daily, 600 mg every 12h x 2, and 600 mg every 8h x 3 were administered. An additional cohort received 600 mg as a cross-over fasted and fed (high fat breakfast).

Results: AZD5847 was generally well tolerated after iv infusion except for local venous irritation. After oral administration, nausea was most frequent adverse event which occurred after higher doses but less frequent with food. There were no significant laboratory or ECG abnormalities.

Key pharmacokinetic parameters (gmean (CV%))

Parameter	600 mg iv (n=5)	600 mg oral fasted (n=7)	600 mg oral fed (n=7)	1200 mg oral fasted (N=6)
Cmax (µg/mL)	16.55 (24.97)	2.60 (18.9)	5.66 (18.2)	3.54 (37.1)
Tmax (h)	0.5	4.00 (1.50–6.07)	5.00 (4.00–6.00)	3.50 (2.00–5.00)
AUC (µg·h/mL)	94.18 (14.12)	38.4 (24.8)	68.7 (17.6)	46.6 (42.7)
CL or CL/F (L/h)	6.42	15.6 (24.7)	8.73 (17.6)	25.7 (42.6)
t1/2 (h)	6.69	8.85 (6.7)	7.52 (9.0)	11.2 (42.7)

Conclusion: AZD5847 was well tolerated. Increase in plasma exposure with oral administration was less than dose proportional, with food increasing oral bioavailability. The flexible design allowed dosing multiple times per day in the initial study. The observed PK and tolerability suggest potential utility for treatment of TB.

Introduction

AZD5847 is an oxazolidinone antibiotic that exerts an antibacterial effect by inhibition of bacterial protein synthesis. AZD5847 when tested on *M. tuberculosis* (Mtu) against laboratory strains and clinical isolates that are singly resistant to front-line anti-tuberculosis drugs demonstrated an MIC_{90} of 1 µg/mL and bactericidal activity of 2 µg/mL with activity against both fast- and slow-growing organisms. In addition, both extracellular and intracellular anti-Mtu has been demonstrated. In a mouse model of inhaled Mtu, a 1 log reduction in colony forming units was achieved with an $AUC_{(0\text{-}24)}$ /MIC of 100.

In toxicological testing, AZD5847 had only minor hematological effects (decrease in WBCs and RBCs) without any effect on the bone marrow. There was no hepatic histological effect. On cardiovascular testing no effect was observed after oral administration but prolongation of the QT interval in the dog was seen after intravenous administration.

In a screen for interaction with a battery of receptors the only positive effect was inhibition of monoamine oxidase with a Ki = 0.08 µg/mL.

Methods

- Two different studies, the intravenous (iv) and the oral study with two parts: Part 1 dose escalation; Part 2: food effect

Intravenous study

- Healthy male volunteers
- Double-blind, placebo-controlled, parallel, dose-escalating
- Drug: disodium phosphate salt of AZD5847 which rapidly converts to AZD5847
- Doses: 60, 200 and 600 mg
- Infusion: 30 minutes
- Drug concentration:
  - 40 mg/mL for the 60 and 200 mg dose
  - 2 or 6 mg/mL for the 200 and 600 mg dose
- Two cohorts of 8 subjects (6 active, 2 placebo) receiving either 2 or 3 doses
- ECGs with QT intervals locally read

Oral study

- Healthy male volunteers

Part 1 dose escalation

- Design: double-blind, placebo-controlled, parallel with separate cohorts of 8 subjects (6 active, 2 placebo) per dose level
- Doses: 50, 100, 200, 600, 1200, 1200 (600 mg every 12 hours x 2) and 1800 mg (600 mg every 8 hours x 3)
- ECGs: digital, obtained over 24 hours with central reading of intervals

Part 2 food effect

- Design: open-label, cross-over with a cohort of 8 subjects
- Dose: 600 mg
- Fasted vs. fed [a high caloric (800 to 1200 calories), high fat (50%) breakfast]

Common methodologies in both studies

- Safety review committee comprising of the investigator, study physician, pharmacokineticist and senior clinical pharmacologist reviewed the available data before dose escalation and deciding on next dose.

Parameters

- Periodic plasma samples for PK
- Safety monitoring – vital signs, laboratory values, adverse events

Analysis of AZD5847 plasma concentration

- AZD5847 was determined after liquid–liquid extraction followed by high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS-MS). The method was linear with a range of 5–100 ng/mL (iv study) and 5–5000 ng/mL (oral study) with a lower limit of quantification of 5 ng/mL.

Registration

- The studies predated public study registration. The AstraZeneca clinical trial number is D3430C00001.

Results

Demographics	Age, years Mean (range)	Weight, kg Mean (range)	BMI, Kg/m^2 Mean (range)	Race (Caucasian/ Black/Am. Indian)
Intravenous study (n=16)	36.2 (21–50)	80 (56–101)	25.4 (19.8–28)	16/0/0
Oral study Part 1 (n = 56)	26.2 (18–45)	79.2 (58.4–98.8)	25.2 (18.9–29.5)	29/27/0
Oral study: Part 2 (n = 8)	29.5 (19–44)	75.3 (64.3–92.1)	24.2 (19.9–30.2)	2/5/1

Safety and Tolerance

(treatment related)

There were no serious adverse events and only one subject withdrew after receiving 600 mg x 3 orally.

Intravenous study:

- 40 mg/mL concentration: 7 of the 9 subjects experienced arm discomfort in the infusion arm ± a rash and redness of the vein above the infusion site
- 2 to 6 mg/mL concentration: 4 of 10 subjects reported pain and/or rash at or above the infusion site.

Oral study:

Part 1 – Dose escalation: The following table summarizes the reported treatment-related adverse events

Preferred Term, n (%)	Placebo n=14	AZD5847, mg 50 n=6	100 n=6	200 n=6	600 n=6	600 x 2 n=6	600 x 3 n=6	1200 n=6
Any AE	2 (14)	2 (33)	0	1 (17)	0	2 (33)	2 (33)	1 (17)
Nausea	0	0	0	0	0	1 (17)	1 (17)	1 (17)
Dizziness	0	0	0	0	0	1 (17)	0	1 (17)

One subject withdrew after receiving the 600 mg x 3 because of moderate intensity of syncope, dizziness, nausea, and vomiting

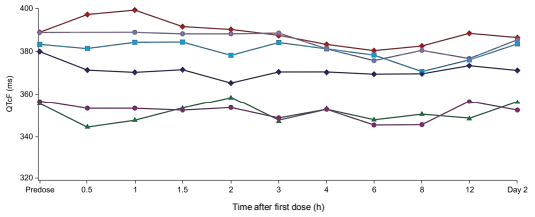
Part 2 – Food effect cross-over:

Fasting: 3 of 8 reported nausea and 1 of 8 headache

Fed: 1 of 8 reported nausea and 1 of 8 headache.

No effect was observed on the electrocardiograms (including ECG intervals)

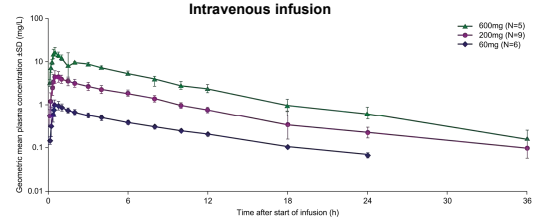
QTc intervals of individual subjects administered 600 mg x 3



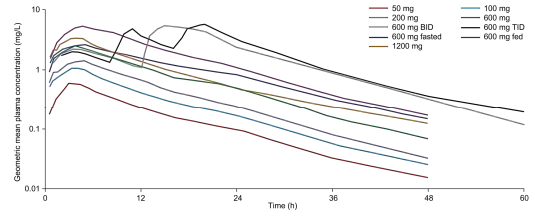
No effect was observed on vital signs and routine laboratory monitoring

Pharmacokinetics

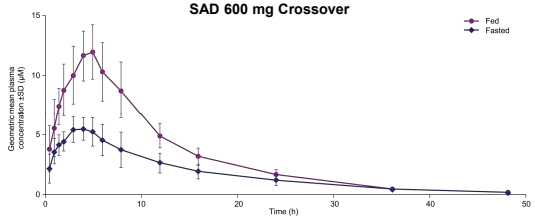
Intravenous infusion



Oral pharmacokinetics; mean data, all groups studied



SAD 600 mg Crossover



Pharmacokinetic parameters after intravenous administration

Mean (CV%) for AUC and Cmax; mean (standard deviation) for $t_{1/2}$, CL, and V_{ss}

Variable	60 mg (n=6)	200 mg (n=9)	600 mg (n=5)
AUC (µg·h/mL)	7.28 (5.2)	31.6 (19.2)	94.2(14.1)
C_{max} (µg/mL)	1.04 (22.2)	4.83 (28.4)	16.6 (25.0)
$t_{1/2}$ (h)	7.2 (0.67)	7.12 (2.03)	6.69 (1.09)
CL (L/h)	8.25 (0.42)	6.43 (1.22)	6.42 (0.85)
V_s (L)	78.5 (11.64)	55.3 (12.08)	50.0 (4.67)

Pharmacokinetic parameters after oral administration

Mean (CV%)

Variable	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)	600 mg (n=6)	600 mg x 2 (n=5)	600 mg x 3 (n=5)	1200 mg (n=6)
AUC[a] (µg·h/mL)	7.43 (7.8)	13.6 (17.1)	19.7 (14.0)	36.4 (15.8)	103 (17.2)	130 (27.8)	46.6 (42.7)
C_{max}[b] (µg/mL)	0.594 (8.3)	1.10 (14.6)	1.45 (11.9)	2.71 (27.1)	5.68 (12.5)	5.87 (28.6)	3.54 (37.1)
t_{max}[c] (h)	3.50	4.00	4.00	3.50	16.00	19.00	3.50
$t_{1/2}$ (h)	9.18 (6.4)	8.65 (3.8)	8.32 (10.5)	8.96 (15.7)	7.63 (10.5)	8.48 (7.5)	11.2 (42.7)
CL/F[a] (L/h)	6.73 (7.9)	7.34 (17.3)	10.1 (14.3)	16.5 (15.8)	11.7 (17.1)	13.8 (27.9)	25.7 (42.6)
V_z/F[a] (L)	89.1 (9.7)	91.6 (15.2)	122 (7.3)	213 (20.3)	129 (20.5)	169 (35.5)	414 (32.1)

a – based on total dose; b – highest concentration during the day; c – median value

Food effect after the administration of 600 mg (part 2)
Statistical analysis of Fed/Fasted Ratio

Parameter	Fed*	Fasted*	Ratio, %	90% CI
AUC (µg·h/mL)	68.8	37.8	182	(157.66, 209.84)
C_{max} (µg/mL)	5.69	2.59	220	(187.78, 258.29)

*Geometric least square mean

Conclusion

- AZD5847 administered orally during a single day was well tolerated but local tolerance was poor after intravenous administration.
- The pharmacokinetics were linear but less then proportional when administered orally after an overnight fast.
- Food significantly increased the bioavailability by an average of 80% after a 600 mg dose.
- The flexible design allowed dosing multiple times per day in the initial oral study and inclusion of a food effect study. When combined with the iv study, a dose regimen was determined to test in efficacy clinical trials.
- The observed PK and good tolerability at predicted therapeutic exposure of AUC/MIC_{90} >100 suggest potential utility for treatment of TB.

Acknowledgments

- Dr. D. Sandall from AstraZeneca who was the investigator for the iv study and Dr. P. Meier from Quintiles and their staff who implemented the oral study.

References

- See other abstracts being presented at ICAAC: A1-1735, A1-1736, F1-1364
- Gravestock MB *et al*. Bioorg Med Chem Lett 2003;13:4179–86