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Murine Pharmacokinetics and In Vivo Gram-negative Activity of AN3365, A Novel Boron-containing Protein Synthesis Inhibitor.

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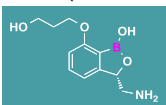
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Introduction

The global rise of multi-drug resistant Gram-negative bacteria necessitates the introduction of truly novel therapeutic agents. AN3365 (GSK2251052), which has successfully completed Phase I clinical trials, is a member of a novel class of boron-containing antibacterial proteins synthesis inhibitors. AN3365 inhibits leucyl-tRNA synthetase (LeuRS) via a novel oxaborole tRNA trapping (OBORT) mechanism (1). Pharmacokinetics and *in vivo* efficacy against Gram-negative bacteria are described.

Figure 1. AN3365 (GSK2251052) chemical structure



Methods

Pharmacokinetic analysis

Female CD-1 mice were dosed at 30 mg/kg IV and SC for PK analysis. Blood was collected retro-orbitally and by cardiac puncture and analyzed using LC/MS/MS. LLOQ = 1 ng/mL.

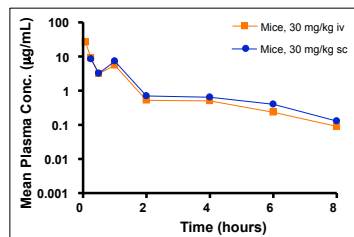
Neutropenic thigh in vivo efficacy

Female CD-1 mice were made neutropenic with IP injections of cyclophosphamide (150 mg/kg) on Days -4 and -1 before infection. 0.1 mL of inoculum was administered to the thigh muscle of each hind leg. Compound was administered subcutaneously at 2 hours post-infection and onwards. Thighs were collected at 2, 4, 6 and 24 hours post-infection and processed to determine CFU/thigh.

References

1. Rock, F., Mao, W., Yaremchuk, A., et al., 2007. Science, 316:1759-1761.

CD-1 Mouse Pharmacokinetics



Formulations for IV and SC: 7.5 mg/mL in Sterile DI Water, pH = 5.02.

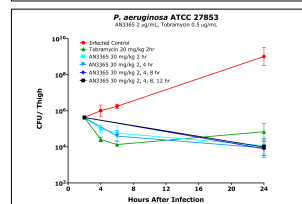
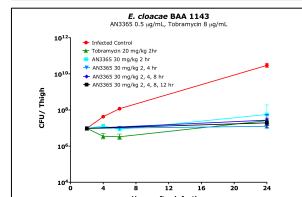
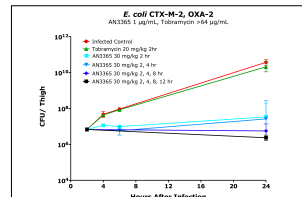
AN3365 IV ¹	IV-30 mg/kg (n=3)
Cmax (µg/mL) @ 5 min	26.0
CL (mL/h/kg)	2914
Vc (mL/kg)	805
Vss (mL/kg)	3895
MRT (h)	1.34
AUC (h*µg/mL)	10.3
α _{1/2} (h) (%AUC)	0.12 [62]
β _{1/2} (h) (%AUC)	2.23 [38]

AN3365 SC ²	SC-30 mg/kg (n=3)
Cmax (µg/mL)	8.4
Tmax (h)	0.25
AUC ₀₋₂₄ (h*µg/mL)	12.1
Terminal t _{1/2} (h)	2.5
Bioavailability (%)	100

¹WinNonlin two-compartment analysis with 1/y² weighting.

²WinNonlin non-compartment analysis with uniform weighting.

Neutropenic-mouse Thigh Model



Summary of Efficacy and PK

Subcutaneous Dose of AN3365	Dose Regimens (hours post-Infection)	Efficacy (Log ₁₀ reduction in CFU vs. vehicle-treated controls at 24 h)						PK Parameter		
		<i>E. coli</i> ATCC 25922	<i>E. coli</i> ESBL (OXA-2, CTX-M2)	<i>E. cloacae</i> BAA-1143	<i>K. pneumoniae</i> ATCC 43816	<i>P. aeruginosa</i> ATCC 27853	Total AUC ₀₋₂₄ (h·µg/mL)	Cmax (µg/mL)	Tmax (h)	
30 mg/kg (dose 1x30)	2	4.00	3.04	2.71	1.79	4.94	12.1	7.45	2.5	
60 mg/kg (dose 2x30)	2, 4	4.07	3.15	3.37	2.64	5.06	24.2	9.38	4.15	
90 mg/kg (dose 3x30)	2, 4, 8	4.02	3.82	3.03	3.06	5.11	36.3	9.38	4.15	
120 mg/kg (dose 4x30)	2, 4, 8, 12	4.08	4.2	3.18	3.56	5.02	48.4	9.38	4.15	
MIC (MIC ₉₀) (µg/mL)	AN3365	1 (1)	1 (1)	0.5 (1)	1 (1)	2 (8)				
MIC (µg/mL)	Tobramycin	1	>64	8	0.5	0.5				

Conclusions

- AN3365 shows favorable *in vivo* pharmacokinetics in mice with good t_{1/2}, AUC and excellent SC bioavailability
- AN3365 shows good *in vivo* activity against MIC₉₀ strains of *E. coli* and *K. pneumoniae*
- A single SC dose (30 mg/kg) of AN3365 is sufficient to prevent growth of *E. coli* ATCC 25922, a derepressed *ampC E. cloacae* and a multidrug-resistant *E. coli* ESBL strain *in vivo*
- A single subcutaneous dose (30 mg/kg) gives a 4.94 log₁₀ CFU reduction with *P. aeruginosa*
- These data demonstrate that the novel antibacterial AN3365 is efficacious *in vivo*