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Safety and Pharmacokinetics (PK) in Humans of Intravenous ETX2514, a β-lactamase Inhibitor (BLI) which Broadly Inhibits Ambler Class A, C, and D β-lactamases.

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Safety and Tolerability

ETX2514 has been generally safe and well tolerated either alone or in combination with SUL and/or IMP/CIL; no significant changes in laboratory or clinical safety parameters were observed in Parts A or B.

Pharmacokinetics

A Phase 1, randomized, placebo-controlled trial in 4 parts (15 cohorts) was conducted to evaluate the PK of ETX2514 alone or in combination with IMP/CIL or SUL in healthy adult male and female subjects (age 18-45 years; N=209). In Parts A and B, healthy adult male and female subjects (N=195) received single dose ETX2514 (1/2/4 g) and SUL (1/2 g) (3h infusion) over time.

Results

ETX2514 PK

Cohort 1: 0.25 g IV ETX2514/placebo infused over 2 hours

Cohort 2: 0.5 g IV ETX2514/placebo infused over 2 hours

Cohort 3: 1 g IV ETX2514/placebo infused over 3 hours

Cohort 4: 2 g IV ETX2514/placebo infused over 3 hours

ETX2514 + SUL PK

Cohort 5: 0.25 g ETX2514 and 0.5 g SUL infused over 2 hours

Cohort 6: 0.5 g ETX2514 and 1 g SUL infused over 2 hours

Cohort 7: 1 g ETX2514 and 2 g SUL infused over 3 hours

Cohort 8: 2 g ETX2514 and 4 g SUL infused over 3 hours

Conclusions

ETX2514 + Imipenem/Cilastatin Drug-Drug Interaction (Cohort 14)

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of ETX2514

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of imipenem/cilastatin

References


5. Entas Therapeutics. 2017; Entas Therapeutics, Waltham, MA.

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Part C: ETX2514-Imipenem/Cilastatin Drug-Drug Interaction (Cohort 14)

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of ETX2514

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of imipenem/cilastatin

Pharmacokinetics

ETX2514 alone or in combination with IMP/CIL or SUL does not alter drug disposition in plasma. ETX2514 single and multiple dose PK is linear and dependent on dose. The relationship between dose and area under the curve (AUC) is dose proportional.

Safety

ETX2514 is generally safe and well tolerated as a single dose up to 2 g and in multiple doses up to 4.8 g when administered alone or in combination with SUL and/or IMP/CIL.

The general safety profile of ETX2514 has not changed when co-administered, as a single dose, with imipenem/cilastatin, with unaltered and unaltered AUC and Cmax.

Abstract

Background

ETX2514 is a novel BLI with broad spectrum activity against Ambler classes A, C, and D β-lactamase enzymes. The addition of ETX2514 to sulfadiazine (SUL), ticarcillin-clavulanate (IMP/CIL), and/or imipenem/cilastatin (IMP/CIL) provides potentially novel therapeutics for the treatment of resistant Pseudomonas aeruginosa and other β-lactamase-producing strains. In vitro, ETX2514 demonstrates excellent activity against carbapenem-resistant A. baumannii and other β-lactam-resistant pathogens.

Methods

A 4-part double-blind, placebo-controlled study (5 cohorts) of ETX2514 administered as a 3 h infusion. Healthy male and female subjects (age 18-55 years) with a single elderly cohort (age 65 years) were used. Full details of the methods are included in the manuscript. In brief, 135 male and 74 female subjects received 1 g ETX2514 administered as a 3 h infusion over 3 days.

Results

ETX2514 PK

Cohort 1: 0.25 g IV ETX2514/placebo infused over 2 hours

Cohort 2: 0.5 g IV ETX2514/placebo infused over 2 hours

Cohort 3: 1 g IV ETX2514/placebo infused over 3 hours

Cohort 4: 2 g IV ETX2514/placebo infused over 3 hours

ETX2514 + SUL PK

Cohort 5: 0.25 g ETX2514 and 0.5 g SUL infused over 2 hours

Cohort 6: 0.5 g ETX2514 and 1 g SUL infused over 2 hours

Cohort 7: 1 g ETX2514 and 2 g SUL infused over 3 hours

Cohort 8: 2 g ETX2514 and 4 g SUL infused over 3 hours

Conclusions

ETX2514 + Imipenem/Cilastatin Drug-Drug Interaction (Cohort 14)

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of ETX2514

• Co-administration of ETX2514 and imipenem/cilastatin did not alter the PK of imipenem/cilastatin

Pharmacokinetics

ETX2514 alone or in combination with IMP/CIL or SUL does not alter drug disposition in plasma. ETX2514 single and multiple dose PK is linear and dependent on dose. The relationship between dose and area under the curve (AUC) is dose proportional.

Safety

ETX2514 is generally safe and well tolerated as a single dose up to 2 g and in multiple doses up to 4.8 g when administered alone or in combination with SUL and/or IMP/CIL.

The general safety profile of ETX2514 has not changed when co-administered, as a single dose, with imipenem/cilastatin, with unaltered and unaltered AUC and Cmax.