Clinical Evaluation of SYN-004, an Oral Beta-Lactamase Inhibitor for the Prevention of Antibiotic-Induced Disruption of Intestinal Microflora


Abstract

Antibiotics that are excrated into the intestine, such as ceftriaxone (CRO), can damage the microbiota and inactivate a disease such as Clostridium difficile. SYN-004, a recombinant β-lactamase inhibitor, was assayed in animals for oral efficacy to prevent the microbiota by degrading bacterial antibiotic. SYN-004 was administered orally to expand the hydrolysis of β-lactam to cephalosporins, including CRO, while maintaining antibacterial activity.

SYN-004 was manufactured in 2 kg, was formulated into entero-coated pellets. In vitro, the pellets retained CRO activity for more than 1 week. SYN-004 activity was reconstituted for 7 days in vitro, demonstrating stability in a disodium succinate salt formulation. CRO (500 mg/kg) administered orally to dogs by nebulization 2 days before administration of SYN-004 (400 mg/kg) protected the CRO against degradation, and SYN-004 protected the CRO against exposure to the hydrolysis of β-lactam to cephalosporins, including CRO, while maintaining antibacterial activity.

Clinical Evaluation of SYN-004 was initiated in 2011 with single ascending and multiple ascending dose pharmacokinetics, safety and tolerability studies in humans. A phase I clinical study in healthy volunteers was initiated in 2012 to assess intravenous β-lactam degradation. The clinical study included assessment of SYN-004, a recombinant β-lactamase inhibitor, in a phase I clinical study in healthy volunteers. The clinical study was designed to assess the safety, tolerability, and PK profile of SYN-004 in healthy adults.

SYN-004 was safe and well tolerated at doses up to 750 mg/kg/day for 28 days in dogs.

Minimal systemic SYN-004 was detected in dogs, SYN-004 was no longer orally active at 100 mg/kg, SYN-004 was not immmunogenic at the clinical doses tested.

Phase 1: Single Ascending Sequential Dose Safety, Tolerance, and PK Study

Clinical Evaluation of SYN-004: Phase 1 Studies in Healthy Adults

Phase 2a clinical studies of SYN-004 were initiated in 2015 and a Phase 2b clinical study is expected to begin in 2H 2015.

Conclusions

In dogs, oral delivery of SYN-004 pellets resulted in efficient degradation of intestinal ceftriaxone.

Phase 1: Single Ascending Sequential Dose Safety, Tolerance, and PK Study

Study 1: Twenty-Eight Day Oral SYN-004 Dosing Study

Study 2: Fourteen Day SYN-004 Dosing Study with IV Ceftriaxone Administration

Assess the safety, tolerability and PK profile of SYN-004 in healthy adults.

Blood samples for PK evaluation and anti-SYN-004 Abs were collected at 24 subjects randomised 1:1 to CRO (275 mg/kg IV qd x 3 days) or control (CRO PBO 275 mg/kg IV qd x 3 days). The two groups were not interfered with normal activities and received without intervention. The TEAEs of pyrexia and of headache in different patients, were both observed on microscopy only, and at CRO received without intervention. SYN-004 was not systemically bioavailable even with dosing four times the proposed clinical dose, and the plasma concentrations tended to occur in the 2-hr post-dose and the peak concentrations were at or near the assay LLOQ (0.96 ng/ml). CRO dosing did not result in any prolongation of exposure to SYN-004 levels. No anti-SYN-004 antibodies were detected in the subjects.

Results

SYN-004 was safe in Two GLP Toxicology Studies in Dogs

This dog study was initiated in April 2011 with single ascending and multiple ascending dose pharmacokinetics, safety and tolerability studies in humans. A phase I clinical study in healthy volunteers was initiated in 2012 to assess intravenous β-lactam degradation. The clinical study included assessment of SYN-004, a recombinant β-lactamase inhibitor, in a phase I clinical study in healthy volunteers. The clinical study was designed to assess the safety, tolerability, and PK profile of SYN-004 in healthy adults.

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Phase 2a clinical studies of SYN-004 were initiated in 2Q 2015 and a Phase 2b clinical study is expected to begin in 2H 2015.

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