

## Pharmacokinetic Characterization of the Novel Pulmonary Delivery Excipient Fumaryl Diketopiperazine

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### Abstract

#### Background:

Technosphere® [Bis-3,6(4-fumarylaminobutyl)-2,5-diketopiperazine (FDKP)] microparticles, the integral component of the Technosphere inhalation system, deliver drugs to the deep lung and have been used to administer insulin and glucagon-like peptide-1 via inhalation in clinical studies. Three studies were conducted to characterize FDKP pharmacokinetics, including assessments in subjects with diabetic nephropathy (DNP), in subjects with chronic liver disease (CLD), and in healthy subjects.

#### Methods:

An open-label, nonrandomized, two-period, fixed-sequence crossover absorption, distribution, metabolism, and excretion (ADME) study was conducted in six healthy nonsmoking men who received single intravenous and oral doses of [<sup>14</sup>C]FDKP solution, with serial sampling of blood, urine, feces, and expired air. Additionally, two single-dose, open-label, parallel-design studies with 20 mg of inhaled FDKP were conducted in (1) 12 diabetic subjects with normal renal function and 24 DNP subjects and (2) 12 healthy subjects and 21 CLD subjects.

#### Results:

In the ADME study, >95% of the intravenous dose and <3% of the oral dose were recovered in urine, with no evidence of metabolism. No significant pharmacokinetic differences were observed between healthy subjects and CLD subjects [geometric mean (% coefficient of variation) area under the curve from time 0 to 480 minutes ( $AUC_{0-480}$ ): 26,710 (34.8) and 31,477 (28.8) ng/ml·min, respectively]. Maximum observed drug concentration ( $C_{max}$ ) and  $AUC_{0-480}$  were higher in DNP subjects than in subjects with normal renal function [ $C_{max}$ : 159.9 (59.4) ng/ml versus 147.0 (44.3) ng/ml;  $AUC_{0-480}$ : 36,869 (47.2) ng/ml·min versus 30,474 (31.8) ng/ml·min]. None of the differences observed were considered clinically significant.

#### Conclusions:

Fumaryl diketopiperazine is predominantly cleared unchanged by the kidney with essentially no oral bioavailability. Technosphere is a safe delivery vehicle for medications administered via inhalation.

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**Abbreviations:** (ADME) absorption, distribution, metabolism, and excretion, ( $AUC_{0-480}$ ) area under the curve from time 0 to 480 minutes, ( $AUC_{0-\infty}$ ) area under the curve from time 0 to infinity, ( $AUC_{0-t}$ ) area under the curve from time 0 to  $t$ , (BMI) body mass index, ( $C_{last}$ ) last observed insulin concentration, (CLD) chronic liver disease, ( $C_{max}$ ) maximum observed drug concentration, (DNP) diabetic nephropathy, (FDKP) Bis-3,6(4-fumarylaminobutyl)-2,5-diketopiperazine, (GFR) glomerular filtration rate, (HPLC) high-performance liquid chromatography, (LSC) liquid scintillation counting, ( $t_{1/2}$ ) terminal elimination half-life, ( $t_{last}$ ) time corresponding to last observed drug concentration, ( $t_{max}$ ) time to maximum observed drug concentration

**Keywords:** chronic liver disease, diabetic nephropathy, fumaryl diketopiperazine, inhalation, Technosphere®

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