An Open-Label, Single Dose Study to Investigate the Absorption, Distribution, Metabolism, and Elimination of [14C]-LCZ696 and Its Metabolites in Healthy Male Subjects
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Purpose
LCZ696 is a novel angiotensin receptor neprilysin inhibitor (ARNI). Upon oral administration, LCZ696 provides exposure to AHU377 and valsartan. The primary objectives of this study were to determine the pharmacokinetics and routes of excretion of LCZ696, 200 mg, to quantify the metabolites of the AHU377 in plasma, urine and feces, and to elucidate key biotransformation and clearance pathways of AHU377 in humans.

Methods
This study employed an open-label design with a single oral 14C-radiolabeled dose of LCZ696, 200 mg. Four healthy male subjects were enrolled and completed the study as planned.

Results
1. Mass balance (~100%) was achieved in this study.
2. Cmax of total radioactivity in blood and plasma was achieved within 1 to 2 hours. The mean terminal half-life of elimination (T1/2) for blood and plasma radioactivity was 10.1 and 8.11 hours, respectively.
3. The mean half-life of AHU377 delivered by LCZ696 was 1.31 h, and the mean apparent clearance (CL/F) was 49.4 L/h with a mean apparent volume of distribution (Vz/F) of 82.7 L.
4. The major metabolite of AHU377 was LBQ657 (ester hydrolysis product) accounting for ~37% of plasma radioactivity.
5. AHU377 elimination was primarily in the form of its metabolite LBQ657, with unchanged AHU377 in urine and feces accounting for only 0.8 – 2.8 % and 0.3 – 0.9 % of the dose, respectively.
6. 51.7 – 67.8 % of the AHU377-related dose was recovered in urine and 36.9 – 48.3 % of the dose was recovered in feces, both primarily as LBQ657.

Conclusion
The AHU377 analyte of LCZ696 is primarily eliminated through renal excretion (60%), predominantly in the form of the major metabolite LBQ657. LCZ696 200 mg was safe and well tolerated.