

9th Euro-Global Summit on

Toxicology and Applied Pharmacology

June 22-24, 2017 Paris, France

An engineered pH sensitive PCSK9 antibody to enhance pharmacokinetic and pharmacodynamic properties

Pamela Garzone, Matteo Levisetti, Tenshang Joh, Hong Wan, Hong Liang, Barry Gumbiner and Javier Chaparro-Riggers
Pfizer Inc., USA

Introduction & Aim: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor (PCSK9) binds to and down regulates low-density lipoprotein receptor (LDL-R) levels on hepatocytes, resulting in LDL-cholesterol (LDL-C) lowering. A PCSK9 monoclonal antibody (mAb) was engineered with pH-sensitive binding to enhance pharmacokinetic (PK) and pharmacodynamics (PD) properties.

Methodology: In men and women (18–70 years) with hypercholesterolemia and prescribed statins, single 0.3, 1, 3, or 6 mg/kg subcutaneous (SC) RN317 doses or 1, 3, and 6 mg/kg intravenous (IV) were evaluated. Three doses of 300 mg SC every 28 days (Q28d) were also evaluated in another cohort. Key exclusion criteria included poorly controlled diabetes and hypertension.

Results: In humans, absorption was slow and varied, reaching the maximum concentration (C_{max}) between 3 and 10.5 days after RN317 SC. The half-life was long (~19–21 days). Absolute bioavailability ranged from 38.5% to 67.5%. Accumulation with repeated dosing was minimal ($R_{ac}=1.23$). The most frequent adverse events (AEs) were upper respiratory tract infection (n=5), headache (n=4), and diarrhea (n=4). Mean percentage decreases from baseline in LDL-C ranged from 0.2% to 52.5% across the RN317 dosages compared with 5.9% to 15.3% with placebo and maintained to day 29. The magnitude and duration of LDL-C reduction with IV RN317 was generally greater than that observed after SC. Following 3.0 mg Q28d, minimal fluctuation in LDL-C lowering (trough-to-nadir ratio>0.9) was noted throughout the study period.

Conclusions: A long terminal half-life and sustained LDL-C lowering was observed; the mean % LDL-C reduction observed was not as marked as that with other anti-PCSK9 mAbs following single or multiple doses. RN317 was well-tolerated and consistent in safety profile with other anti-PCSK9 mAbs, suggesting the tolerability profile of the drug was not altered with the engineered changes.

Biography

Pamela Garzone has 5 years of teaching and research experience at the University of Pittsburgh. She has worked in the biotech-pharma industry in preclinical and clinical positions, having increasing responsibilities over this time. She has extensive drug development experience in therapeutic areas such as oncology, hematology, immunology, neuroscience, and cardiovascular and infectious diseases. She joined Pfizer in 2009 as an Executive Director and became the Clinical Team Lead for the Early Development Programs at Rinat, a research unit of Pfizer. In 2015, she was promoted to VP, Group Asset Team Lead, responsible for the development strategy of assets within the Oncology Research Unit. In addition, she is currently the Interim Head of the Early Oncology Development and Clinical Research Group.

pamela.garzone@Pfizer.com

Notes: