European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 07, 2014

Development of a decision-making biomarker for CRTH2 antagonism in clinical studies„

Daniel S. Strasser; Herve Farine; Martin Holdener; Jochen Zisowsky; Rene Roscher; Julie Hoerner; Martine Gehin; Patricia N. Sidharta; Jasper Dingemanse; Peter M.A. Groenen

Abstract

Biomarkers have shown to improve success rates in the development of novel drugs, providing essential information in the early phases of clinical development for decision-making. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is pursued as a drug target for a number of inflammatory diseases. CRTH2 antagonists block the activation and migration of key inflammatory cells such as eosinophils, basophils, and Th2 cells. The mechanism of action of CRTH2 antagonists was established in cells isolated from human blood. Biomarkers derived from these experiments were included in clinical studies to investigate the mechanism of action and potency of CRTH2 antagonists in human. For clinical phase I studies with the CRTH2 antagonist ACT-453859, a follow-up molecule of setipiprant, inclusion of the most precise and robust pharmacodynamic (PD) biomarker with a clinically relevant target effect was desired to aid phase II dose selection. Candidate biomarkers such as IL-13 secretion from Th2 cells and CRTH2, CD11b and CD203 modulation on basophils and eosinophils in whole blood were compared in terms of signal intensity and variability. Blockade of CRTH2 receptor internalization was finally chosen as PD biomarker and rigorously tested in a feasibility study. The assay showed excellent robustness, an intra-assay precision of 5% and inter-subject variability smaller than 15%. Based on phase II clinical study results with setipiprant, 90% CRTH2 receptor blockade was defined as clinically relevant PD effect. This target PD effect provides the means to take decisions based on the data generated in the phase I clinical studies with ACT-453859. Focal points • Bedside Biomarkers offer a great potential to influence decisions taken during early clinical development. For clinical phase I studies with the CRTH2 antagonist ACT-453859, a follow-up molecule of setipiprant, inclusion of a biomarker was desired to aid phase II dose selection. In order to facilitate decision-making, we developed a biomarker that delivers high quality data under clinical circumstance and defined a relevant target biomarker effect. • Benchside In-vitro experiments with human whole blood identified CRTH2 receptor internalization on basophils and eosinophils as the most precise and robust biomarker. Clinical results obtained with setipiprant in a seasonal allergic rhinitis study were used to define the clinically relevant target biomarker effect of 90% CRTH2 receptor blockade. Proof for the chosen target biomarker effect remains to be demonstrated in phase II clinical studies with ACT-453859.

Keywords:

Decision making biomarkerReceptor internalizationCRTH2GPR44PTGDR2ACT