INTRODUCTION

Background

- Ponesimod (ACT-128800) is a potent, orally active, selective sphingosine-1-phosphate 1 (S1P1) receptor modulator including rapid, dose-dependent, and reversible reduction of circulating lymphocytes.1
- Ponesimod was shown to be effective in phase II trials in psoriasis and multiple sclerosis2,3.
- Population pharmacokinetic (PK) models that characterize the PK of ponesimod and its metabolites including the influence of hepatic/renal dysfunction may be relevant for safety evaluations in organ-impaired subjects.

Objectives

- Characterization of the PK of ponesimod and its primary metabolites, M12 and M13, in healthy and hepatically and renally impaired subjects.
- Covariate screening to assess the influence of subject characteristics on the PK.

METHODS

Data

- Five phase I studies including healthy (N=112), hepatically impaired (N=3×8 with mild, moderate, and severe hepatic impairment), and renally impaired (N=2×8 with moderate and severe renal impairment) impaired subjects.
- Data from single and multiple doses and an up-down titration regimen, an intravenous (i.v.) and an oral (p.o.) formulation in the dose range from 5 to 100 mg i.d. were pooled. In total, 3618, 3415, and 3314 concentrations from 152 subjects (91 male and 61 female) were available for ponesimod, M12, and M13, respectively.
- The mean age of all subjects was 39 years (range: 20 to 60 years) and the mean body weight was 76 kg (range: 46 to 113 kg).

Modeling

- Non-linear mixed effects modeling, parameter estimation with SAEM.
- Monolix (version 4.31), R (version 3.0.2), and Berkeley Madonna4,5 (version 8.3.18).

RESULTS

- The PK of ponesimod and its metabolites are characterized by two-compartment models for each of the analytes with 1st order absorption including lag time connected via a liver compartment. Elimination was best described by a 1st order process, whereas drug metabolism was saturable (Figure 1).
- Body weight was found to have a significant effect on both volumes of distribution for ponesimod. Hepatic function significantly affected ponesimod metabolism as well as the elimination of all three analytes (Table 1). Renal impairment showed no significant effect.
- Overall, the observed concentrations show a good correspondence with the model-predicted concentrations (Figure 2).
- Figure 3 illustrates the population typical concentration-time profiles of ponesimod and its metabolites following repeated dosing of 10 mg for 30 days in healthy and severely hepatically impaired subjects. Exposure in a severely hepatically impaired compared to a healthy subject at steady state is 3.6x, 8.4x, and 2.7x higher for ponesimod, M12, and M13, respectively.

CONCLUSIONS

- The population PK model developed for ponesimod and its primary metabolites characterized the data well.
- Hepatic function was found to have a strong impact on the clearance of ponesimod and its metabolites.
- The model may serve as a valuable tool for the future drug development process, safety evaluation, and dose adaptation in hepatically impaired subjects.

REFERENCES