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Population pharmacokinetics of ponesimod and its primary metabolites in healthy and organ-impaired subjects

Dominik Lott [a,b,*], Andreas Krause [b], Jasper Dingemanse [b], Thorsten Lehr [a]

[a] Saarland University, Department of Clinical Pharmacy, Saarbrücken, Germany
[b] Actelion Pharmaceuticals Ltd, Department of Clinical Pharmacology, Allschwil, Switzerland

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ABSTRACT

Ponesimod, a selective, orally active $S1P_1$ receptor modulator, reduces total blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs. It is currently in clinical development for the treatment of relapsing-remitting multiple sclerosis. Ponesimod has two primary metabolites, M12 and M13, that circulate in human plasma.

The work presented in this paper predicts and quantifies the accumulation of ponesimod and both metabolites in healthy and organ-impaired subjects. Based on clinical data including studies in renally and hepatically impaired subjects, a population pharmacokinetic (PK) model was developed to characterize the PK of ponesimod and its primary metabolites and to qualify and quantify the influence of organ impairment on the concentration-time profiles of these compounds. As hepatic and renal function are critical for the elimination of the majority of drugs, being able to quantify their influence is important for the treatment in these populations.

The PK of ponesimod and its metabolites were characterized by 2 compartments for each of the analytes, interconnected via a liver compartment that serves as a physiologically meaningful approach to model first-pass metabolism. Absorption and elimination were described by first-order processes whereas metabolism was found to be saturable at supratherapeutic doses. Body weight and hepatic impairment were identified as significant covariates. Whereas the effect of body weight is small and within the margins of between-subject variability, hepatic impairment markedly affects the PK of ponesimod and its metabolites with up to 9-fold higher steady-state exposure in subjects with severe hepatic impairment.

1. Introduction

Ponesimod is an orally active, selective modulator of the sphingosine 1-phosphate receptor 1 ($S1P_1$) that induces a rapid, dose-dependent, and reversible reduction in total blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs (Piali et al., 2011). As $S1P_1$ receptors play a central role in lymphocyte trafficking, targeting them represents a new therapeutic approach to treat diseases with an autoimmune component such as psoriasis and multiple sclerosis (Matloubian et al., 2004; Schwab et al., 2005; Vaclavkova et al., 2014). Ponesimod has been shown to be effective in the treatment of relapsing-remitting multiple sclerosis in a phase 2 clinical trial and recently entered a phase 3 trial to demonstrate efficacy and safety in a large patient population over a long treatment period (ClinicalTrials.gov, 2015; Olsson et al., 2014).

The pharmacokinetics of ponesimod were shown to be dose-proportional with a time to maximum concentration ranging from 2 to 4 h and a half-life of approximately 32 h (Brossard et al., 2013). As ponesimod induces dose-dependent desired (lowering total lymphocyte counts) as well as undesired (lowering heart rate following first doses) effects, administration of the optimal dose/dosing regimen plays a key role in the treatment with ponesimod (Brossard et al., 2014; Hoch et al., 2015; Scherz et al., 2015).

In humans, two primary metabolites of ponesimod, M12 and M13, circulate in plasma, with M13 being the predominant metabolite and considered to be safety-relevant due to its abundance in plasma of more than 10% of drug-related material (Reyes et al., 2015). M12 is formed via oxidation of a terminal ethylene glycol side chain while the formation of M13 also involves the loss of one carbon atom (Fig. 1). M12 and M13 are the only circulating metabolites in humans and can undergo various secondary metabolic transformations. Ponesimod is primarily eliminated via fecal excretion, urinary excretion plays a minor role (Reyes et al., 2015).

Although the metabolites do not contribute to the efficacy of ponesimod, exposure to them might be relevant for the safety of the treated subjects, particularly in cases when drug accumulation following repeated dosing plays a role, e.g., in subjects with impaired metabolism such as hepatically and renally impaired subjects.

A population pharmacokinetic(s)/pharmacodynamic(s) (PK/PD) model that describes the PK of ponesimod with a 2-compartment

* Corresponding author at: Department of Clinical Pharmacy, Saarland University, 66123 Saarbrücken, Germany.
E-mail address: Dominik.Lott@uni-saarland.de (D. Lott).

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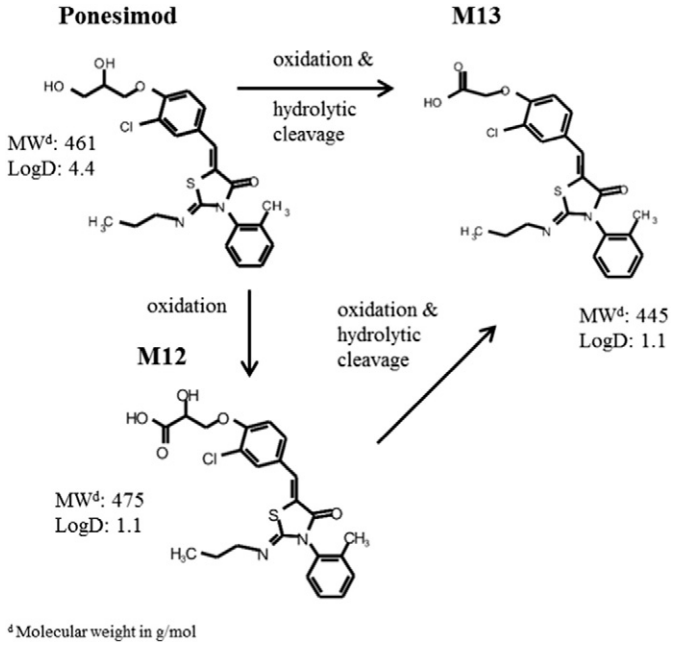

Fig. 1. Proposed metabolic scheme of ponesimod to M12 and M13.

model with sequential zero/first-order absorption, absorption lag time, and linear clearance was developed previously and used to quantify the effect of exposure on total lymphocyte count (PK/PD relationship) (Krause et al., 2014). However, the primary metabolites M12 and M13 were not included in this model due to limited metabolite measurements. Furthermore, special-population studies, i.e., in renally and hepatically impaired subjects, were not available at the time. Including the primary metabolites as well as the data generated in organ-impaired subjects in the population model might be beneficial to evaluate treatment with ponesimod in subjects with organ impairment.

The objectives of this analysis were to develop a population PK model that characterizes the concentration-time profiles of ponesimod and its primary metabolites M12 and M13 including between-subject variability. In addition, the influence of subject-specific factors (covariates) were to be qualified and quantified, particularly with regard to the influence of organ impairment. Once developed, the model was used to simulate dosing scenarios that have not been tested clinically, e.g., multiple-dose administration in organ-impaired subjects, which in turn can be used for safety evaluations and potential dose adaptations.

2. Methods

2.1. Subject and data set properties

The underlying analysis data set comprised the data from five clinical studies in which ponesimod as well as metabolite concentrations were measured (Table 1). The studies comprised single-dose studies in healthy and organ-impaired subjects as well as up-titration studies in healthy subjects. The doses administered ranged from 10 mg (single-dose studies) to up to 100 mg (up-titration studies) and included an oral as well as an intravenous (i.v.) formulation. All doses were given once daily (o.d.). Pooling the studies led to a wider range of doses/dosing regimens and increased the diversity of the subjects' characteristics with respect to their demographics such as age and body weight. Furthermore, the inclusion of special-population studies in renally and hepatically impaired subjects allowed to investigate the influence of organ impairment on the concentration-time profiles of ponesimod, M12, and M13.

Table 1
Summary of the analysis data set.

Study number/variable	109	110	112	113	114	Total
Study type	Up-titration, double-blind	Up-titration, double-blind	Single-dose, open-label	Single-dose, open-label	Single-dose, open-label	Up-titration, single-dose
No. subjects	12	53	32	24	17	138
No. conc. records:						
(total/above LLOQ)	1671/1610	3710/3710	1644/1212	1152/869	2142/1656	10319/9057
• Ponesimod	557/544	1399/1399	548/491	384/333	714/667	3602/3434
• M12	557/525	1216/1216	548/384	384/235	714/451	3419/2811
• M13	557/541	1095/1095	548/337	384/301	714/538	3298/2812
Doses (mg)	10–20–40–60–80–100	10–20–40–60–80–100	10	10	5, 10	5, 10, 20, 40, 60, 80, 100
Formulation	Tablets	Tablets	Tablets	Tablets	Tablets i.v. solution	Tablets i.v. solution
Age (years)[a]	27 (22–52)	34 (20–45)	54 (30–58)	51 (34–60)	27 (22–40)	39 (20–60)
Weight (kg)[a]	71 (61–97)	79 (58–101)	75 (51–113)	69 (46–101)	77 (64–93)	76 (46–113)
Male, n[b]	7 (58%)	43 (74%)	18 (56%)	6 (25%)	17 (100%)	91 (66%)
Healthy subjects	12 (100%)	53 (100%)	8 (25%)	8 (33%)	17 (100%)	98 (71%)
Hepatic impairment[c]:						
• Mild	–	–	8 (25%)	–	–	8 (5.8%)
• Moderate	–	–	8 (25%)	–	–	8 (5.8%)
• Severe	–	–	8 (25%)	–	–	8 (5.8%)
Renal impairment[d]:						
• Moderate	–	–	–	8 (33%)	–	8 (5.8%)
• Severe	–	–	–	8 (33%)	–	8 (5.8%)
Race, n[b]						
• Caucasian	11 (92%)	32 (60%)	32 (100%)	24 (100%)	17 (100%)	116 (84%)
• Black	–	20 (38%)	–	–	–	20 (15%)
• Asian	1 (8%)	1 (2%)	–	–	–	2 (1%)

[a] Median and range.
[b] Number of subjects.
[c] Classified according to Child-Pugh score (Pugh et al., 1973).
[d] Classified according to the glomerular filtration rate as obtained from the MDRD equation (Levey et al., 1999; Levey et al., 2006).