

Pharmacokinetics, Pharmacodynamics and Safety of Mocravimod After Single and Multiple Oral Dosing in Healthy Japanese Participants

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Abstract

Aim

Mocravimod is a selective sphingosine-1-phosphate receptor-1 (S1P₁) modulator with immunomodulatory properties. This phase I study evaluated the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple oral doses of mocravimod in healthy Japanese adults.

Methods

This single-centre, randomized, double-blind, placebo-controlled, ascending-dose study comprised a single-dose part (0.3–3.0 mg) and a multiple-dose part (1.2 or 2.0 mg once daily for 28 days). Blood concentrations of mocravimod and its active metabolite mocravimod-phosphate were quantified using validated LC–MS/MS methods. PK parameters were derived using non-compartmental analysis. Pharmacodynamic assessments included peripheral blood lymphocyte counts, heart rate assessed by Holter electrocardiography, and evaluation of white blood cell subsets. Safety was evaluated throughout the study.

Results

Sixty-four participants were enrolled (single dose, n = 40; multiple dosing, n = 24). Systemic exposure to mocravimod and mocravimod-phosphate increased with dose following both single and multiple dosing. Median time to maximum concentration ranged from 6–10 hours after single dosing, and steady state was achieved by Day 28 during multiple dosing. The apparent terminal half-life following single dosing ranged from approximately 104–139 h for mocravimod and 109–136 h for mocravimod-phosphate. Mocravimod induced dose-dependent, reversible peripheral lymphopenia and transient decreases in heart rate. All adverse events were mild, with no serious adverse events or study discontinuations.

Conclusions

Mocravimod demonstrated predictable pharmacokinetics, expected pharmacodynamic effects and good tolerability in healthy Japanese participants. The findings were consistent with prior observations in non-Japanese populations, supporting further clinical development.

What is already known about this subject

- S1P₁ receptor modulators reduce circulating lymphocyte counts through receptor-mediated sequestration in lymphoid tissues.

- In non-Japanese populations, mocravimod has shown dose-dependent immunomodulatory activity with an acceptable safety and tolerability profile.

What this study adds

- This study characterizes the pharmacokinetic and pharmacodynamic profile of mocravimod in healthy Japanese participants.
- Mocravimod produced dose-dependent, reversible reductions in peripheral lymphocyte counts and transient decreases in heart rate, consistent with S1P₁ receptor modulation.
- The findings support pharmacokinetic and pharmacodynamic comparability between Japanese and previously studied non-Japanese populations.

Introduction

Mocravimod is a synthetic immunomodulatory agent that is rapidly phosphorylated *in vivo* to mocravimod-phosphate, the active metabolite that selectively modulates sphingosine-1-phosphate (S1P) receptors, with strong affinity for subtypes 1 and 5 (S1P₁/S1P₅) [1]. Functional antagonism of S1P₁ results in receptor internalization and sequestration of lymphocytes within secondary lymphoid organs, leading to reduced circulating lymphocyte counts and suppression of immune cell trafficking.

Sphingosine 1-phosphate (S1P) receptor modulators have substantially changed the management of immune-mediated diseases, including multiple sclerosis (MS), through selective control of lymphocyte trafficking. Fingolimod, the first drug in this class, demonstrated that functional antagonism of the S1P isoform 1 (S1P₁) receptor promotes lymphocyte retention in secondary lymphoid organs, thereby reducing their release into the bloodstream and diminishing pathogenic immune responses [1]. This mechanism underpins the clinical benefit of S1P modulators in MS and has driven the development and regulatory approval of several second-generation agents—siponimod, ozanimod, ponesimod, and etrasimod—for MS and ulcerative colitis. Compared with fingolimod, these newer compounds show greater receptor selectivity and more favourable safety profiles [1–4]. Ongoing research is evaluating S1P receptor modulators in a wide range of disorders, including neurodegenerative and inflammatory diseases, consistent with their ability to regulate immune-cell migration without causing generalized immunosuppression [2, 5].

In previous clinical studies conducted outside Japan, mocravimod demonstrated dose-dependent reductions in circulating lymphocytes, transient reductions in heart rate and an overall favourable safety profile [6, 7].

An extensive clinical programme has characterized the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of mocravimod and mocravimod-phosphate predominantly in healthy Western participants [6, 7]. Given potential inter-ethnic differences in drug disposition, characterization of mocravimod in Japanese participants was needed to support global clinical development. Previous studies investigated mocravimod in a predominantly Caucasian [7] or mixed population [6]. The present

phase I study was therefore designed to evaluate the tolerability, PK, and PD of single and multiple oral doses of mocravimod in healthy Japanese participants.

Cytochrome P450 (CYP) 3A4 was found to be the major enzyme responsible for the oxidative biotransformation of mocravimod based on in vitro studies and animal data. Average CYP3A4 activity appears to be broadly comparable between East Asian populations, including Japanese and Chinese individuals, and populations of European ancestry [8, 9]. Therefore, major interethnic differences in mocravimod pharmacokinetics driven by CYP3A4-mediated metabolism were not expected.

This manuscript reports the results of the phase I study evaluating mocravimod after single and multiple oral dosing in healthy Japanese participants.

Materials and methods

Study design and ethical conduct

This was a single-centre, randomized, double-blind, placebo-controlled, parallel-group, ascending-dose phase I study conducted in healthy Japanese adults. The study comprised two sequential parts: a single-dose study and a multiple-dose study. The single-dose part evaluated oral mocravimod at doses of 0.3, 1.0, 2.0 and 3.0 mg. The multiple-dose part evaluated mocravimod at doses of 1.2 and 2.0 mg once daily for 28 days (Fig. 1). Dose escalation proceeded only after review of safety data from the preceding dose step. The multiple-dose part was initiated after confirmation of tolerability in the highest single-dose step. The study was conducted at Shinanozaka Clinic, Tokyo, Japan, in accordance with the Declaration of Helsinki, Japanese Good Clinical Practice guidelines and the approved study protocol. The protocol, informed consent form and related study documents were reviewed and approved by the institutional review board. All participants provided written informed consent before any study-specific procedures were performed.

Study population

Eligible participants were healthy Japanese men and women aged 20–55 years, with a body mass index between 18.5 and 25.0 kg/m². Subjects were considered healthy on the basis of medical history, physical examination, vital signs, electrocardiography and clinical laboratory testing at screening and admission. Female participants were required to be surgically sterile, postmenopausal or otherwise not of childbearing potential as defined in the protocol.

Key exclusion criteria included smoking; clinically relevant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, neurological, ophthalmological or immune-system disorders; clinically significant abnormalities in laboratory tests, electrocardiography or pulmonary function; recent use of prescription or over-the-counter medication; recent participation in another clinical trial; recent blood donation; positive tests for hepatitis B, hepatitis C, HIV or syphilis; and, for the multiple-dose study, negative

varicella-zoster virus IgG serology. Subjects with a history of drug or alcohol abuse, pregnancy or breastfeeding, or any condition judged by the investigator to compromise safety or protocol compliance were also excluded.

Randomization and masking

Within each dose step, subjects were randomized to receive mocravimod or matching placebo. The study was double-blind: participants, investigators and study personnel involved in clinical assessments remained unaware of treatment allocation. Placebo capsules were matched to active capsules to maintain blinding. Emergency code-break procedures were available but were not intended for routine use.

Treatment administration

mocravimod and matching placebo were supplied as oral capsules. In the single-dose study, all participants received a pre-assignment placebo dose on Day – 1, followed by a single post-assignment dose of mocravimod or placebo on Day 1. mocravimod doses were 0.3, 1.0, 2.0 or 3.0 mg. Active and placebo treatments were administered orally with 200 mL of water after an overnight fast.

In the multiple-dose study, participants similarly received a pre-assignment placebo dose on Day – 1. From Day 1, subjects received mocravimod 1.2 mg, mocravimod 2.0 mg or placebo once daily for 28 days. The Day 1 dose was administered under fasting conditions; doses from Day 2 to Day 28 were administered within 30 minutes after breakfast. Fasting and water-restriction requirements around dosing were applied according to the protocol.

Pharmacokinetic assessments

Blood samples for pharmacokinetic analysis were collected at prespecified time points after single dosing and during multiple dosing, including intensive sampling after dosing and trough sampling during repeated administration. Concentrations of mocravimod and its active phosphorylated metabolite, mocravimod -phosphate, were determined in whole blood using validated liquid chromatography–tandem mass spectrometry methods (Table S1 and S2).

In the single-dose study, blood samples were collected at the following time points: Days 1 to 5: pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post-dose; Days 7, 10, and 15: at the same time as the dosing time on Day 1 (20 time points in total).

In the multiple dose study, blood samples were collected at the following time points: Days 1 and 14: pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 16 hours post-dose; Days 2, 4, 8, 12, 15, 18, 21, and 24: pre-dose; Days 28 to 32: pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 96 hours post-dose; Days 35, 38, and 42: at the same time as the dosing time on Day 28 (51 time points in total).

Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin Version 6.1. For the single-dose study, parameters included lag time (T_{lag}), time to maximum observed concentration (T_{max}), maximum observed concentration (C_{max}), area under the concentration–time curve extrapolated to infinity (AUC_{inf}) and apparent terminal half-life ($t_{1/2}$). For the multiple-dose study, parameters calculated on Days 1, 14 and 28 included T_{max} , C_{max} , AUC_{0-24} and $t_{1/2}$.

Pharmacodynamic assessments

Pharmacodynamic assessments focused on parameters related to the expected mechanism of S1P₁ receptor modulation. Peripheral blood lymphocyte counts were measured at scheduled time points before and after dosing in both study parts. In the single-dose study, post-dose lymphocyte values were compared with corresponding baseline values obtained before dosing. In the multiple-dose study, lymphocyte counts were evaluated relative to the pre-dose value on Day 1 and followed during treatment and recovery after treatment discontinuation.

Heart rate was assessed using Holter electrocardiography. Mean heart rate, nadir heart rate and changes from baseline were summarized over predefined time intervals. In the multiple-dose study, additional white blood cell subset analyses were performed to characterize treatment-related changes in circulating immune-cell populations, including T-cell, B-cell, monocyte and natural killer cell subsets.

Safety assessments

Safety was evaluated throughout the study by monitoring adverse events, adverse drug reactions, clinical laboratory tests, vital signs, physical examination, neurological examination, pulmonary function testing, 12-lead electrocardiography and Holter electrocardiography. Ophthalmological examinations, including assessments relevant to macular oedema, were performed in the multiple-dose study. Adverse events were coded and summarized by treatment group, severity and relationship to study drug. Clinically significant changes in laboratory values, vital signs, electrocardiographic parameters and other safety assessments were evaluated by the investigator.

Analysis populations

The safety analysis set included all subjects who received any study drug. The pharmacokinetic analysis set included subjects who received active mocravimod and had evaluable blood concentration data for mocravimod and/or mocravimod-phosphate. The pharmacodynamic analysis set included all subjects who received post-assignment study drug and had evaluable pharmacodynamic data.

Statistical analysis

Analyses were primarily descriptive. Demographic and baseline characteristics were summarized by study part and treatment group. Continuous variables were summarized using the number of observations, mean, standard deviation, minimum, median and maximum; pharmacokinetic exposure parameters were summarized using geometric means where appropriate. Categorical variables were summarized as counts and percentages. Pharmacokinetic parameters were summarized by dose group and study day. Pharmacodynamic parameters, including lymphocyte counts and heart-rate measures, were summarized by treatment group and time point. For peripheral blood lymphocytes, derived parameters included $E_{\max}$, defined as the maximum observed post-dose absolute lymphocyte count, and AUC_{0-24} , defined as the area under the absolute lymphocyte count–time curve from 0 to 24 hours after dosing, calculated using the linear trapezoidal method. Each parameter was also expressed as a ratio to its corresponding baseline parameter derived from the pre-assignment placebo assessment. Log-transformed $E_{\max}$ and AUC_{0-24} were analysed separately using ANCOVA models with treatment group as a fixed effect and the logarithm of the corresponding baseline parameter as a continuous covariate. Treatment contrasts and two-sided 95% confidence intervals were exponentiated to obtain baseline-adjusted geometric mean ratios versus placebo. For heart rate, derived post-baseline parameters, including maximum effect ($E_{\max}$) and area under the effect–time curve over 24 hours ($AUC_{0-24,post}$), were analysed using ANCOVA models with treatment group as a fixed effect and the corresponding parameter derived from the baseline Holter recording ($E_{\max,0-24,base}$ or $AUC_{0-24,base}$) as a continuous covariate. Treatment effects were summarized as baseline-adjusted least-squares mean differences with two-sided 95% confidence intervals.

Results

Subject disposition and baseline characteristics

A total of 64 healthy participants were enrolled and completed the study (40 in the single-dose part and 24 in the multiple-dose part); all participants were male. Median age was (23–29) years old with a BMI between 20.52 and 22.98 kg/m². No participants discontinued treatment, and no clinically relevant protocol deviations were reported (Table 1).

Table 1. Demographics

All participants were male.

		Part 1 – single dose					Part 2 – multiple dose		
		0.3 mg	1 mg	2 mg	3 mg	Placebo	1.2 mg	2 mg	Placebo
N		8	8	8	8	8	9	9	6
Sex, male, n (%)		8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	9 (100)	9 (100)	6 (100)
Age (years)	Mean	28.5	29.1	27.1	23.3	26.1	27.7	28.9	25.5
	SD	6.2	7.0	7.5	4.6	6.2	4.4	4.5	6.0
Weight (kg)	Mean	62.14	69.59	63.91	61.76	63.20	62.98	64.40	58.77
	SD	5.96	7.50	8.31	6.93	6.35	7.84	4.54	5.97
BMI (kg/m ²)	Mean	20.82	22.98	21.21	20.76	21.27	21.04	21.58	20.53
	SD	1.62	2.12	1.39	1.53	1.72	2.25	1.34	1.18

BMI, body mass index; SD, standard deviation

Pharmacokinetics

Single-dose pharmacokinetics

Mean blood concentration-time profiles of mocravimod and mocravimod-phosphate after single oral doses of 0.3, 1.0, 2.0, and 3.0 mg are shown in Fig. 2A, and corresponding PK parameters are summarized in Table 2. $T_{\max}$ ranged from 6.0 to 10.0 hours across dose levels, although interindividual variability was observed. A small rebound in blood concentrations was noted between $T_{\max}$ and 48 hours after administration. Apparent terminal half-life ranged from approximately 104 to 139 hours for mocravimod and from 109 to 136 hours for mocravimod-phosphate, consistent with first-order elimination. Mocravimod-phosphate was detectable after a short lag time following oral administration, and exposure ratios for $C_{\max}$ and AUC were close to 1 across dose levels.

Table 2

PK parameters of mocravimod and mocravimod-phosphate after single oral dose administration.

Analyte	Parameter	0.3 mg SD	1 mg SD	2 mg SD	3 mg SD
Mocravimod	N	8	8	8	8
	T _{lag} (hr)	1.5 (0.25-3.00)	0.5 (0.00-1.00)	0.375 (0.25-0.50)	0.25 (0.25-0.50)
	T _{max} (hr)	6 (6-12)	8 (2-36)	10 (2-36)	6 (2-36)
	C _{max} (ng/mL)	0.0908 (20.6)	0.249 (20.3)	0.489 (16.7)	0.898 (12.0)
	AUC _{inf} (ng.hr/mL)	NA	48.5 (21.7)	99.9 (31.6)	132 (27.5)
	T _{1/2} (hr)	NA	139 (37.1)	129 (34.4)	104 (20.7)
Mocravimod-Phosphate	N	8	8	8	8
	T _{lag} (hr)	3.5 (2-4)	1.0 (1-2)	1.0 (0.5-1)	0.5 (0.5-1)
	T _{max} (hr)	10 (6-12)	12 (6-36)	10 (6-12)	7 (6-12)
	C _{max} (ng/mL)	0.129 (29.1)	0.335 (23.6)	0.703 (23.3)	1.59 (35.4)
	AUC _{inf} (ng.hr/mL)	NA	56.0 (28.4)	128 (25.7)	190 (36.9)
	T _{1/2} (hr)	NA	124 (16.1)	136 (18.2)	109 (20.9)
AUC, area under the curve; hr, hour; NA, not available, SD, single dose					
Note that Mocravimod AUC _{inf} and T _{1/2} for 1 mg SD were based on N = 6. For AUC _{inf} , T _{1/2} and C _{max} results are shown as geometric mean and CV%. Median (min and max) for T _{max} and T _{lag} .					

Multiple-dose pharmacokinetics

Time-course profiles of the mean concentrations of mocravimod and mocravimod-phosphate in blood after multiple oral administration are shown in Fig. 2B. Pharmacokinetic parameters of mocravimod and mocravimod-phosphate on Days 1, 14 and 28 of multiple oral administration are shown in Table 3. During once-daily dosing, trough concentrations increased gradually, reaching steady state by Day 28 for both analytes. Both C_{max,ss} and AUC_T increased with dose. Apparent terminal half-life values were comparable to those observed after single dosing, and accumulation ratios indicated moderate accumulation with limited fluctuation at steady state.

Table 3

PK parameters of mocravimod and mocravimod-phosphate after multiple oral dose administration.

Analyte		Day1	Day14	Day28	Day1	Day14	Day28
	Parameter	1.2 mg	1.2 mg	1.2 mg	2 mg	2 mg	2 mg
Mocravimod	N	9	9	9	9	9	9
	T _{max} (hr)	2 (2–8)	6 (2–12)	6 (6–8)	2 (2–3)	6 (2–23.5)	6 (4–12)
	C _{max} (ng/ml)	0.481 (13.7)	2.48 (10.2)	2.74 (10.3)	0.552 (22.5)	3.13 (13.2)	3.62 (13.8)
	AUC _{0–24hrs} (ng.hr/ml)	8.16 (14.6)	52.8 (11.1)	58.5 (11.2)	8.92 (17.7)	63.6 (12.2)	76.7 (14.0)
	T _{1/2} (hr)	NA	NA	143 (23.8)	NA	NA	132 (21.3)
Mocravimod-Phosphate	N	9	9	9	9	9	9
	T _{max} (hr)	12 (6–12)	6 (4–23.5)	6 (0–12)	10 (6–12)	6 (4–23.5)	8 (6–12)
	C _{max} (ng/ml)	0.605 (37.5)	3.19 (30.0)	3.58 (29.5)	0.702 (40.9)	4.49 (27.2)	5.21 (22.4)
	AUC _{0–24hrs} (ng.hr/ml)	10.7 (34.6)	67.2 (28.2)	76.5 (30.5)	12.2 (35.5)	91.1 (24.6)	109 (21.6)
	T _{1/2} (hr)	NA	NA	143 (26.8)	NA	NA	130 (21.6)
AUC, area under the curve; hr, hour; NA, not available							
For AUC _{0–24hrs} and C _{max} results are shown as geometric mean and CV%. Median (min and max) for T _{max}							

Table 4
A. Inter-group comparison of the geometric mean ratio to the baseline of ALC (Study 1)

Dose	E _{max} (10 ⁹ /L)	AUC ₀₋₂₄ (hr.10 ⁹ /L)
Placebo	1.00 (0.87–1.14)	1.00 (0.92–1.09)
0.3 mg	0.86 (0.75–0.98)	0.93 (0.85–1.01)
1 mg	0.78 (0.68–0.89)	0.78 (0.71–0.85)
2 mg	0.56 (0.49–0.64)	0.62 (0.57–0.68)
3 mg	0.37 (0.32–0.42)	0.45 (0.41–0.49)
ALC, absolute lymphocyte count; AUC, area under the curve		

Table 4B: Inter-group comparison of the geometric mean ratio to placebo ALC (study 1)

Dose	LS mean E _{max}	LS mean AUC ₀₋₂₄
0.3 mg vs Placebo	0.86 (0.71–1.04)	0.93 (0.82–1.05)
1 mg vs Placebo	0.78 (0.65–0.94)*	0.78 (0.69–0.88)*
2 mg vs Placebo	0.56 (0.46–0.67)*	0.62 (0.55–0.70)*
3 mg vs Placebo	0.37 (0.30–0.44)*	0.45 (0.40–0.51)*

ALC, absolute lymphocyte count; AUC, area under the curve

P<0.05 Model: linear model with dose as fixed effect and log of baseline as covariate

LS mean with 2-sided 95% CI presented.

Pharmacodynamics of peripheral lymphopenia

Single dose

Single-dose administration of mocravimod resulted in dose-dependent reductions in circulating lymphocytes, with maximal decreases observed approximately 10–12 h post-dose and recovery to baseline during follow-up (Fig. 3A). ALC practically returned to the baseline by the study completion assessment (Day 15) at all the mocravimod doses. The numbers of participants whose ALC returned to the baseline at the study completion assessment (Day 15) were 7 (87.5%) out of 8 participants at 0.3 mg, 5 (62.5%) out of 8 participants at 1.0 mg, 3 (37.5%) out of 8 participants at 2.0 mg, 2 (25.0%) out of 8 participants at 3.0 mg, and 7 (87.5%) out of 8 participants at the placebo group. The comparison of the E_{max} and AUC₀₋₂₄ parameters, relative to their baseline value, is shown in Table 4A. Statistically significant differences were found in the ratios to the baseline (logarithmic values) at mocravimod doses

of 1.0 mg or above as compared with those at the placebo administration ($p < 0.05$) for $E_{\max}$ and AUC_{0-24} (Table 4B). At mocravimod doses of 0.3, 1.0, 2.0, and 3.0 mg, geometric mean ratios (least squares means [two-sided 95% confidence interval]) of $E_{\max}$ to the placebo administration were 0.86 (0.71 to 1.04), 0.78 (0.65 to 0.94), 0.56 (0.46 to 0.67), and 0.37 (0.30 to 0.44); and those of AUC_{0-24} were 0.93 (0.82 to 1.05), 0.78 (0.69 to 0.88), 0.62 (0.55 to 0.70), and 0.45 (0.40 to 0.51), respectively. Mocravimod causes dose-dependent lymphocyte lowering, with a clear pharmacodynamic effect starting around 1 mg and progressively stronger effects at 2 and 3 mg.

Multiple dose

During multiple dosing, sustained reductions in ALC were observed, with partial recovery after treatment discontinuation (Fig. 3B). Mean ALC declined from Day 1 and reached maximal reductions from approximately Day 5 through Day 28. At the study completion assessment (Day 49 ± 1), ALC values remained below $1 \times 10^9/L$ in 4 of 9 participants (44.4%) in the 1.2 mg group and 6 of 9 participants (66.7%) in the 2.0 mg group. Maximal decreases from baseline were 79% (95% confidence interval 72% to 84%) and 84% (79% to 88%) in the 1.2 mg and 2.0 mg groups, respectively, versus 19% (-13% to 42%) with placebo. At both mocravimod dose levels, reductions in $E_{\max}$ were statistically significant compared with placebo ($p < 0.05$).

Numbers of participants whose ALC decreased to less than $1 \times 10^9 /L$ at the study completion assessment (Day 49 ± 1) were 4 (44.4%) out of 9 participants at 1.2 mg, and 6 (66.7%) out of 9 participants at 2.0 mg. Maximal decreases (decrease rates from the baseline) in ALC were 79% (72 to 84%) and 84% (79 to 88%) at the KRP-203 doses of 1.2, and 2.0 mg, respectively, and 19% (-13 to 42%) at the placebo administration (least squares mean (two-sided 95% confidence interval)). The maximal decrease in ALC from baseline is shown in Table S3. At both mocravimod doses, statistically significant decreases were found in the logarithm of $E_{\max}$ compared to placebo ($p < 0.01$) (Table S4).

Safety

All adverse events were mild in severity. One participant in part 1 developed mild bacterial diarrhoea. In part 2, 24 participants developed mild adverse events: Alanine aminotransferase increased in 4 participants, blood triglycerides increased in 3 participants, and nasopharyngitis in 2 participants at the 1.2 mg dose, and blood triglycerides increased in 4 participants, Alanine aminotransferase increased in 3 participants, aspartate aminotransferase increased in 2 participants, and gamma-glutamyltransferase increased in 2 participants at the 2.0 mg dose. No serious adverse events, clinically significant laboratory abnormalities or clinically relevant electrocardiographic findings were observed and no participants discontinued treatment due to adverse events.

Heart rate

No cardiac adverse events were reported. Transient decreases in heart rate were observed following both single and multiple dosing. Maximum mean reductions occurred early after dosing, were dose

dependent, and were reversible over time (Fig. 4A). After 28 days of dosing, heart rate remained in the recovery phase (Fig. 4B). After single oral administration, statistically significant differences versus placebo were observed for $E_{\max}$ and AUC_{0-24} across all mocravimod dose levels ($p < 0.05$; Tables S5). Mocravimod 1.2 and 2 mg QD produced a transient reduction in mean 24-hour heart rate, most apparent on Days 2–3, with an approximately 4–7 bpm placebo-adjusted reduction. This effect was no longer evident by Day 5 and was not observed at later assessments (Table S6). Changes in nadir heart rate were inconsistent across dose groups and time points and did not demonstrate a clear dose-dependent or temporally consistent pattern.

White blood cell subsets

White blood cells subset included T cells, Naïve T cells, CD8 + and CD4 + T cells, memory T cells, B cells, NK cells, and monocytes. Multiple dosing led to reversible reductions in circulating T-cell and B-cell subsets and relative increases in monocytes and natural killer cells, consistent with $S1P_1$ -mediated lymphocyte redistribution. Most changes recovered during follow-up. The time-course profile of the mean values of white blood cell subsets is shown in Fig. 5 after multiple oral administration of mocravimod.

Discussion

This study provides the first characterization of the pharmacokinetics, pharmacodynamics, and safety of mocravimod in healthy Japanese participants. Overall, the findings were consistent with prior observations in non-Japanese populations [6, 7], with only minor differences in pharmacokinetic parameters that are unlikely to be clinically meaningful.

In this phase I study, mocravimod demonstrated predictable pharmacokinetics characterized by dose-proportional exposure, a long apparent terminal half-life and moderate accumulation during repeated dosing. These properties are consistent with sustained pharmacological activity and support once-daily dosing. The observed pharmacodynamic effects, including dose-dependent reductions in peripheral blood lymphocyte counts and transient heart rate decreases, are consistent with the known mechanism of $S1P_1$ receptor modulation and align with findings reported for other agents within this drug class. Importantly, these effects were reversible and not associated with clinically significant safety concerns. Overall, the pharmacokinetic, pharmacodynamic and safety profiles observed in healthy Japanese participants were comparable to those previously reported in non-Japanese populations [6, 7], supporting the ethnic generalizability of mocravimod exposure–response relationships.

Median CYP3A4 activity appears to be similar in healthy Japanese and White populations [8, 9], suggesting that PK parameters influenced by CYP3A4-mediated metabolism would also be expected to be similar. Initial population PK analyses identified body weight as a significant predictor of apparent mocravimod clearance; therefore, the trend toward slightly higher $C_{\max}$ and AUC values in Japanese

compared with White participants may be explained by the lower body weight observed in the Japanese population.

Although the effects of S1P receptor modulators on total leukocyte counts are well established, their effects on individual leukocyte subsets in humans are less completely characterized. A recent meta-analysis reported that S1P receptor modulators consistently reduce circulating CD4 + and CD8 + T lymphocytes, including naïve and central-memory subsets, whereas effects on effector-memory T cells and other T-helper subsets, such as Th1 and Th17 cells, remain less consistent or insufficiently studied. Regulatory T-cell data are limited beyond fingolimod. B-cell reductions, including both naïve and memory B-cell populations, appear broadly consistent across indications, while no reproducible treatment-related changes have been identified for circulating monocytes or dendritic cells [10]. The white blood cell subset analysis provides additional mechanistic support for the pharmacodynamic activity of mocravimod. During repeated administration, mocravimod produced a consistent redistribution pattern across lymphocyte subsets, characterized by significant relative reductions in circulating T cells, CD4 + T cells, B cells and naïve CD4 + T cells, together with relative increases in CD8 + T cells, monocytes, natural killer cells and memory CD4 + T cells. This pattern is consistent with the expected pharmacology of S1P₁ receptor modulation, whereby lymphocyte egress from secondary lymphoid organs is inhibited, leading to selective retention of lymphocyte populations that depend on S1P-gradient signalling for recirculation.

The preferential reduction in CD4 + T cells and naïve T cells is particularly relevant, as naïve and central-memory T-cell subsets are known to be more dependent on S1P₁-mediated trafficking than effector-memory populations. In contrast, the relative increase in CD8 + T cells, monocytes and NK cells most likely reflects a shift in the proportional composition of circulating leukocytes rather than true expansion of these subsets. This interpretation is supported by the concurrent reduction in total lymphocyte counts and the absence of comparable changes in the placebo group. The increase in memory CD4 + T cells relative to total CD4 + T cells is also compatible with differential sensitivity of lymphocyte subsets to S1P₁ modulation, with naïve cells being preferentially sequestered.

Most WBC subset changes showed recovery by the end-of-study assessment, indicating reversibility after treatment discontinuation. The exception was the proportion of NK cells among leukocytes at the 2.0 mg dose, which remained elevated at follow-up. Given the small sample size and the proportional nature of the subset analysis, this finding should be interpreted cautiously. It may represent delayed normalization of the leukocyte distribution rather than persistent immune activation or expansion of NK cells. Overall, the subset data are consistent with the primary pharmacodynamic finding of marked but reversible lymphocyte reduction and further support target engagement of mocravimod at both 1.2 and 2.0 mg once daily.

The safety findings were also aligned with the non-Japanese clinical experience with mocravimod. In the present study, adverse events were mild and no serious adverse events, treatment discontinuations, or clinically meaningful safety signals were observed, which is consistent with previously reported healthy-volunteer studies in which the most commonly reported treatment-emergent adverse events were

expected S1P receptor modulator class effects such as bradycardia and decreased lymphocyte count [3].

Following single oral administration, mocravimod produced a statistically significant reduction in mean 24-hour heart rate compared with placebo at doses of 0.3, 1.0, 2.0, and 3.0 mg. The magnitude of the effect increased from 0.3 to 2.0 mg, with placebo-adjusted geometric mean ratios for $E_{\max_{0-24}}$, post of 0.95, 0.89, 0.79, and 0.82, respectively, and corresponding ratios for AUC_{0-24} , post of 0.96, 0.90, 0.83, and 0.83. Thus, the reduction in heart rate appeared to approach a plateau at approximately 2 mg, with no further increase in effect at 3 mg. In the multiple-dose study, reductions in mean 24-hour heart rate were most pronounced on Days 2 and 3 and were no longer apparent by Day 5, suggesting that the heart-rate-lowering effect was predominantly an early and transient pharmacodynamic effect during QD administration.

Several limitations should be considered. This was a small phase I study conducted in healthy Japanese participants, and all enrolled participants were male, which limits generalizability to women, patients and broader clinical populations. The analyses were primarily descriptive and were not designed to formally compare Japanese and non-Japanese populations. In addition, white blood cell subset analyses were conducted in a limited number of participants and should be interpreted as exploratory. Longer follow-up and studies in patient populations are needed to further characterize the durability, reversibility and clinical relevance of the observed pharmacodynamic effects.

Taken together, these findings support the comparability of mocravimod exposure–response relationships between Japanese and non-Japanese populations, while remaining consistent with a predictable, reversible S1P₁-mediated immunomodulatory profile in healthy Japanese participants.

Conclusions

Mocravimod was well tolerated in healthy Japanese participants and exhibited predictable pharmacokinetic and pharmacodynamic profiles consistent with its mechanism of action. The overall PK, PD, and safety findings were comparable to those previously reported in non-Japanese populations, supporting the relevance of these data for global clinical development of mocravimod.

Declarations

Clinical trial registration

This Phase 1 clinical study was conducted in Japan in 2011. Although public clinical trial registries, including the UMIN Clinical Trials Registry, were available at that time, prospective registration was not a requirement applicable to this study under the regulatory and ethical framework in place at study initiation. The study was therefore not prospectively registered, and no clinical trial registration number is available.

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Figures

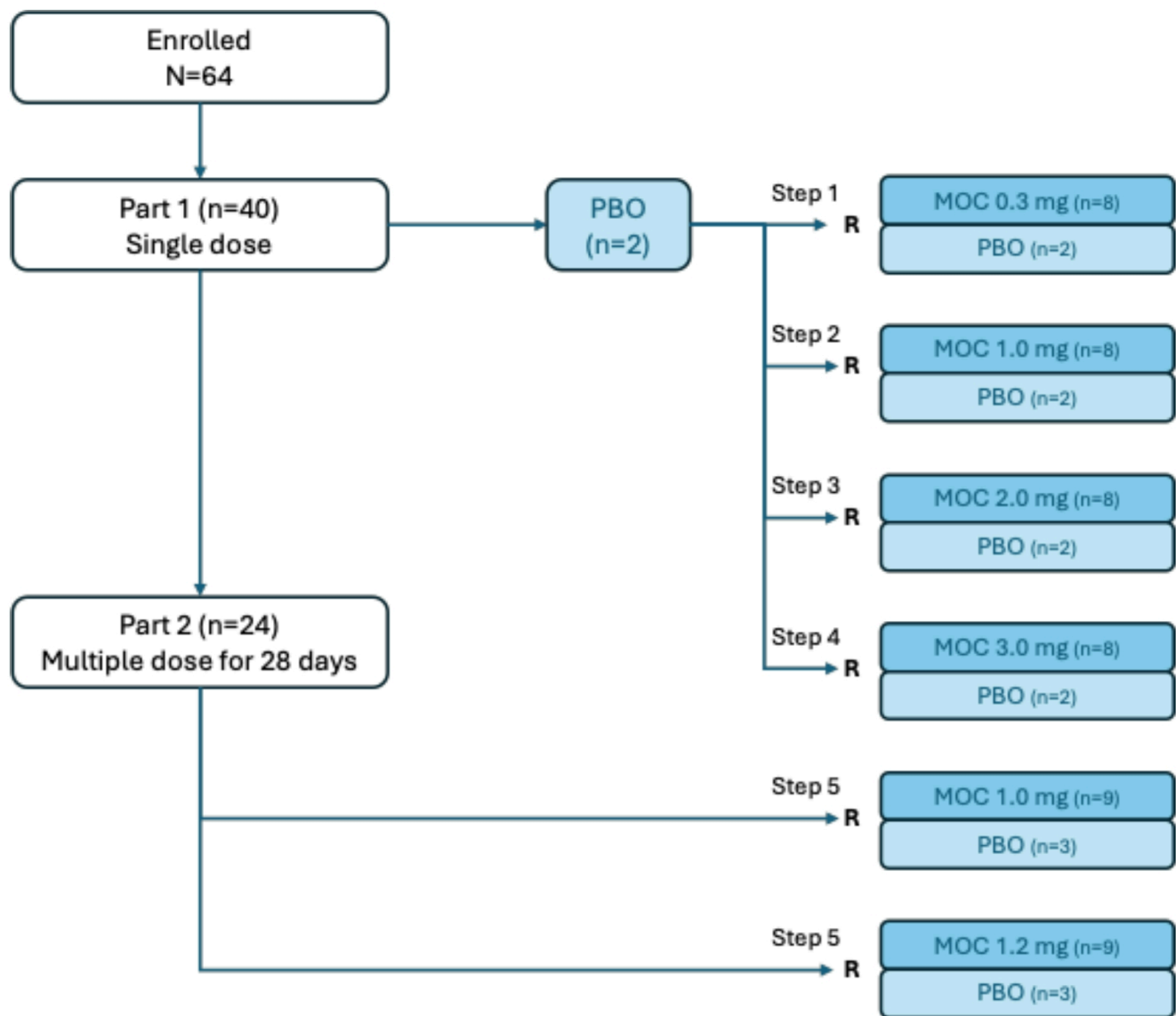
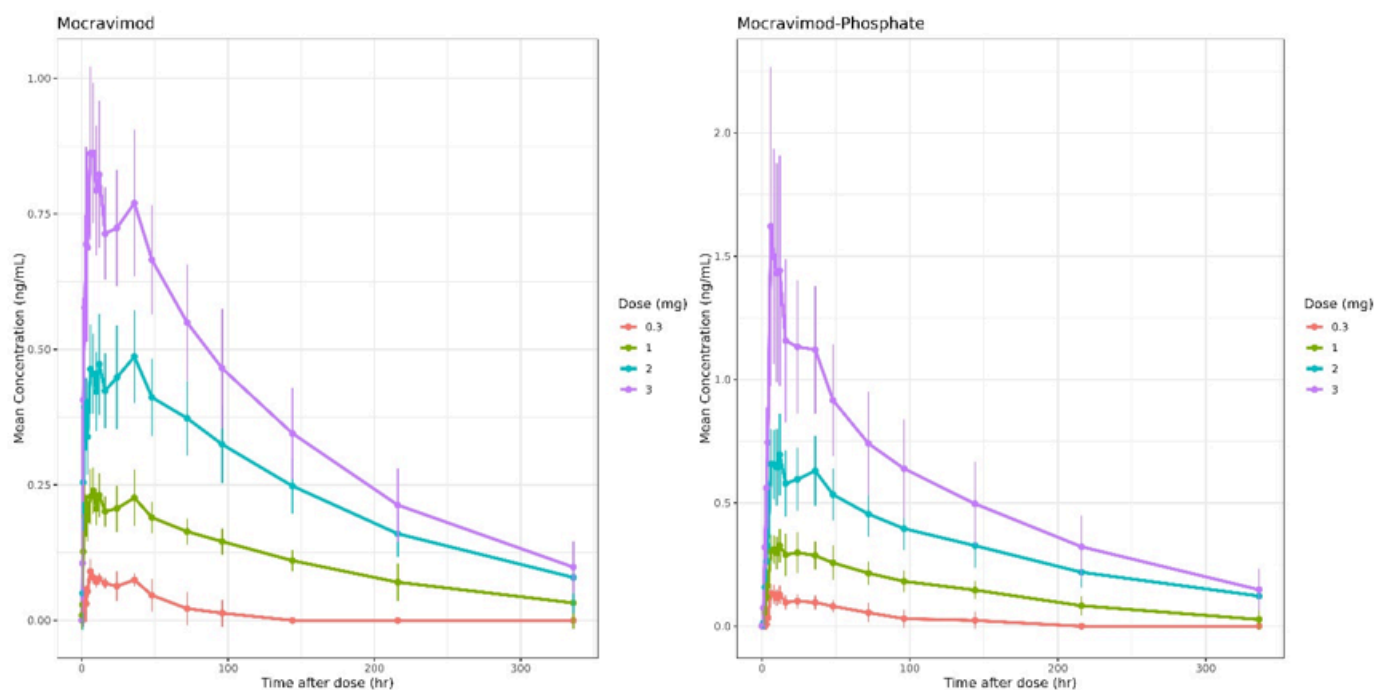


Figure 1

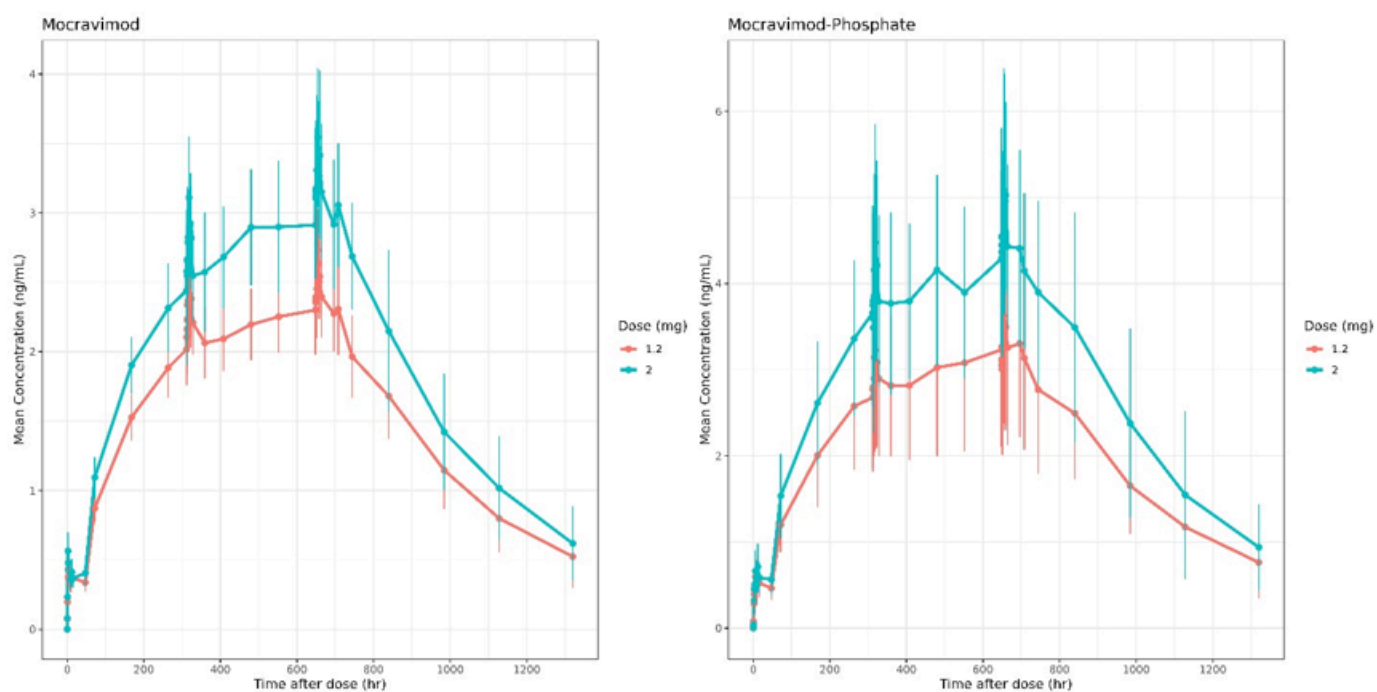
Study design

MOC, mocravimod; PBO, placebo; R, randomization

A

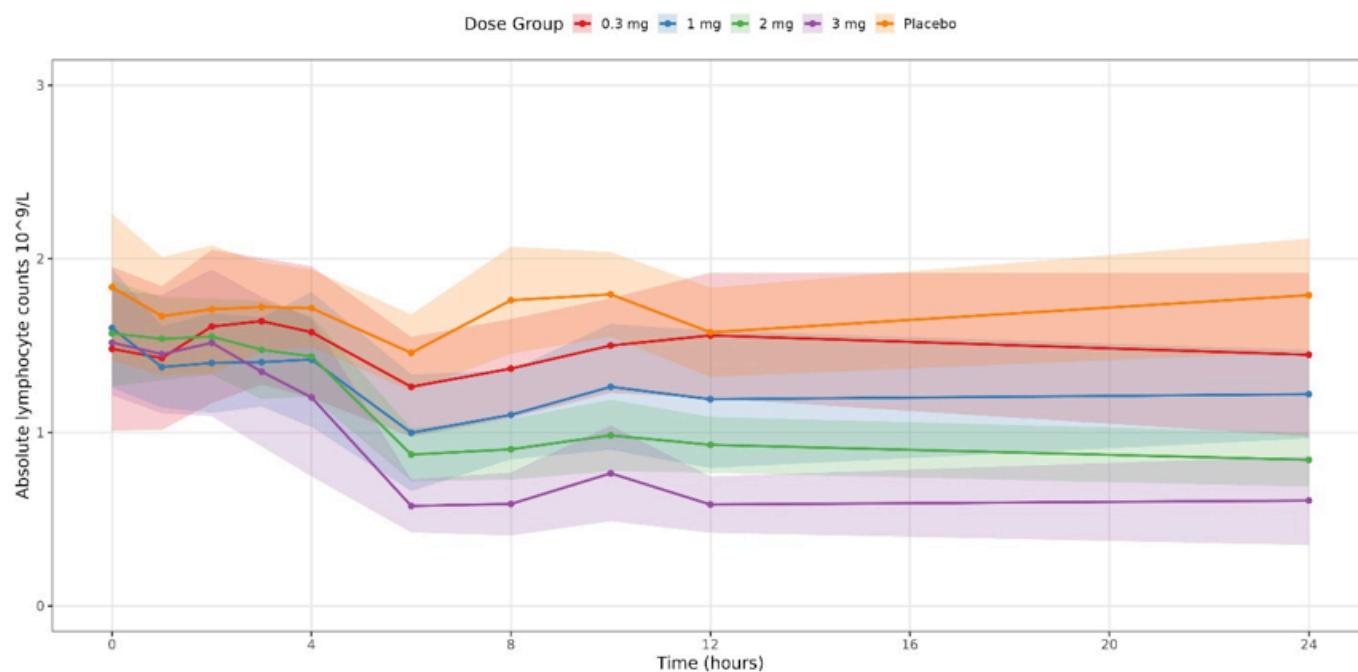


B

**Figure 2**

Time course of blood concentration profiles of mocravimod and mocravimod-phosphate after single dose administration (A) or multiple dose administration (B). Results are shown as mean $\pm$ standard deviation.

A



B

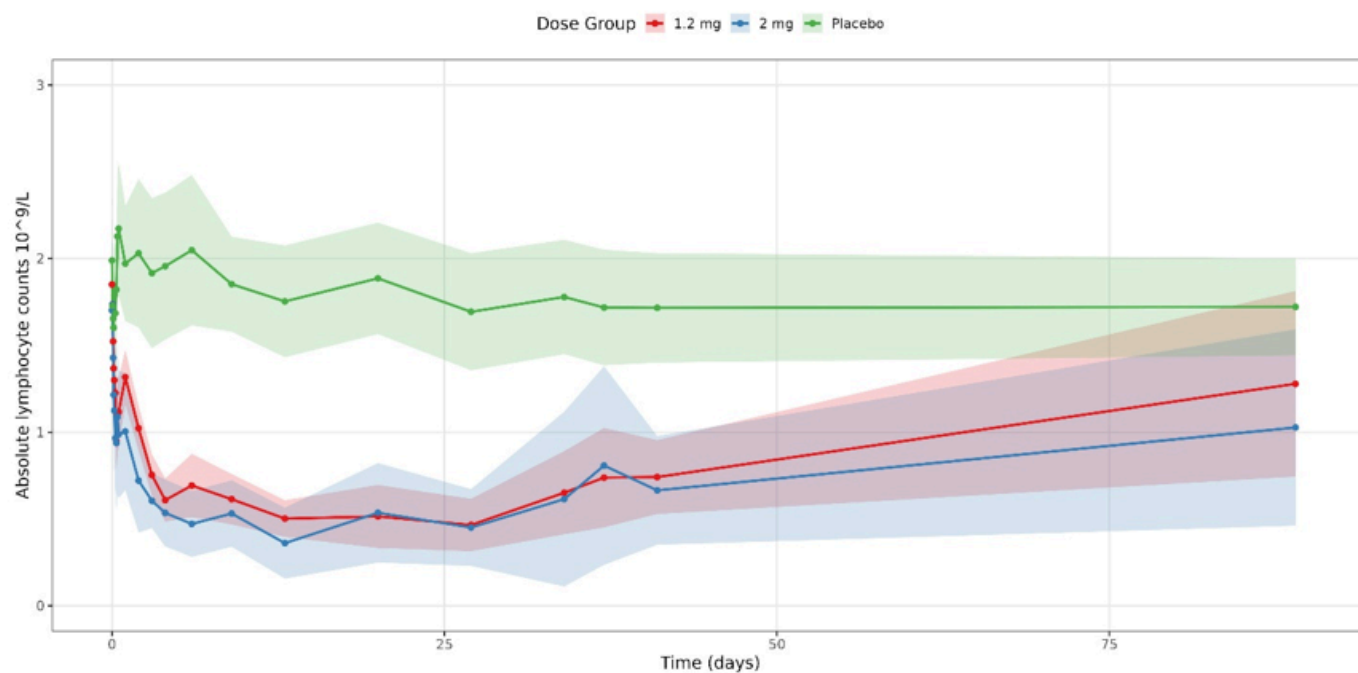
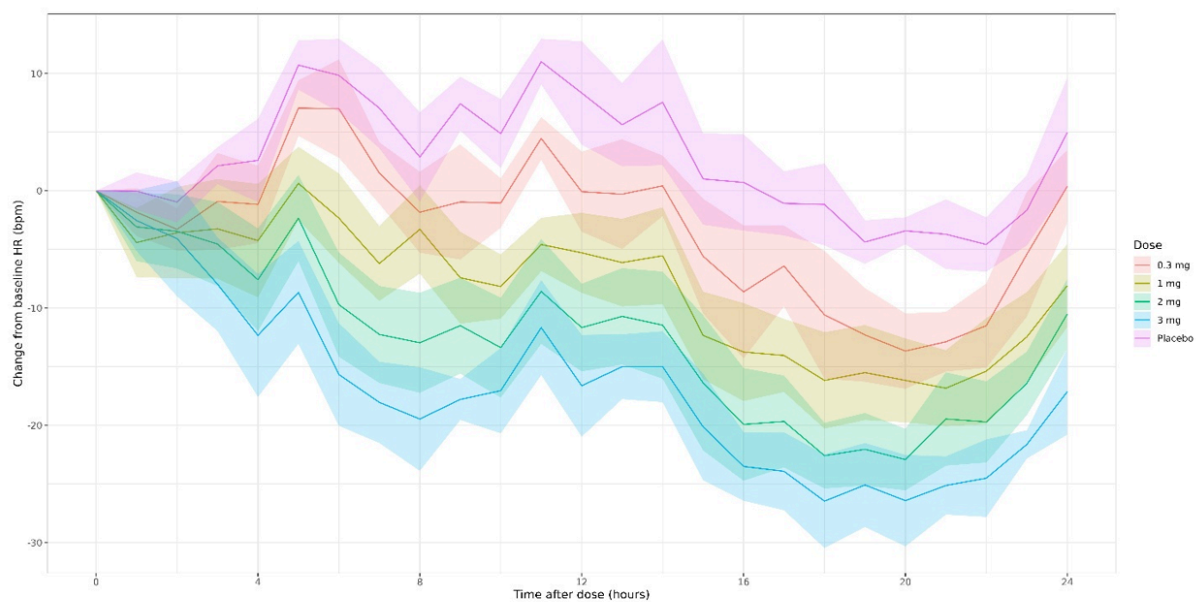


Figure 3

Time course of absolute lymphocyte count profiles after a single dose administration of mocravimod or placebo (A) or multiple dose administration of mocravimod or placebo (B). Results are shown as mean (solid line) and 95% confidence interval (shaded area).

A



B

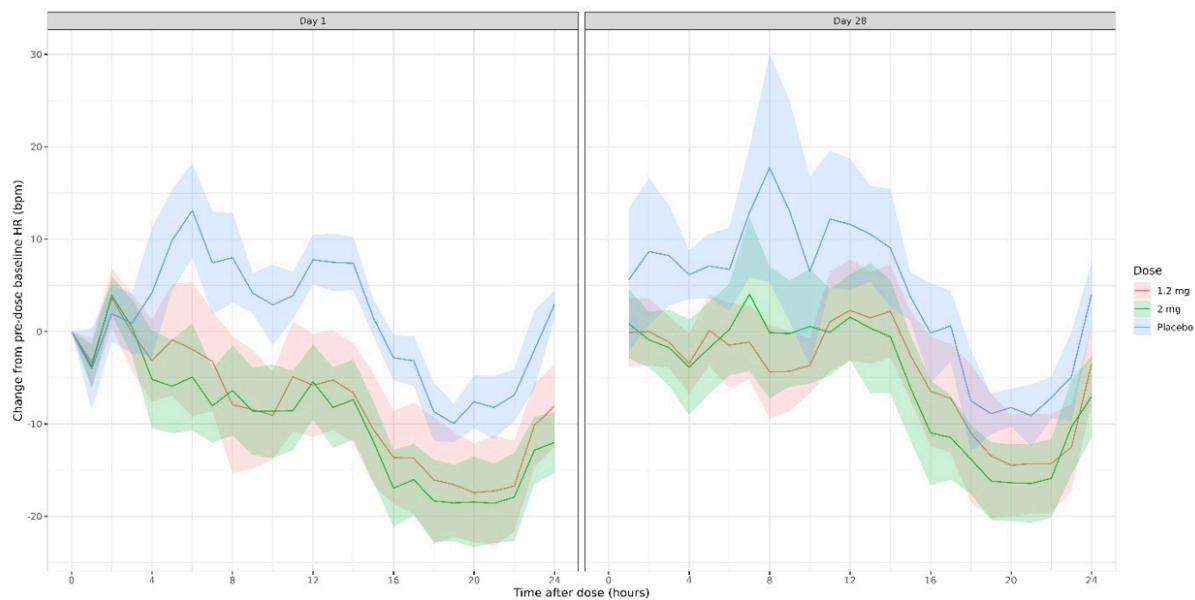


Figure 4

Change from baseline heart rate over time after a single dose administration of mocravimod or placebo (A) or multiple dose administration of mocravimod or placebo on Day 1 and Day 28 (B). Results are shown as mean (solid line) and 95% confidence interval (shaded area).

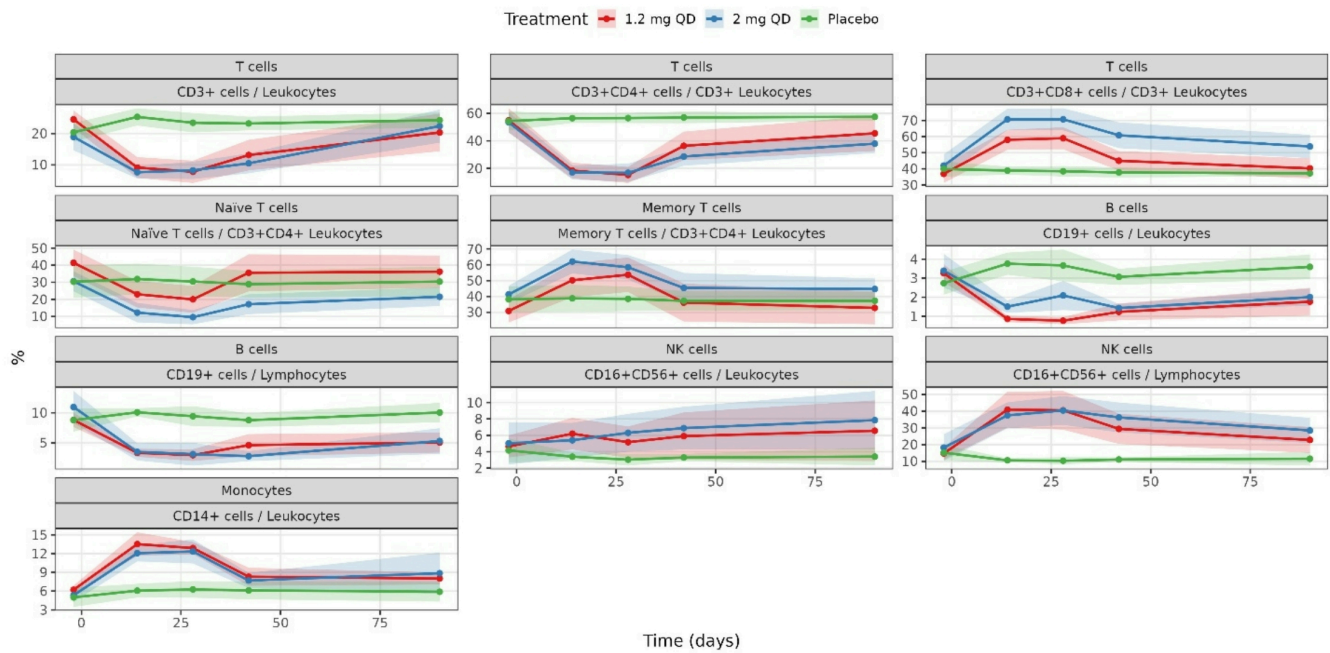


Figure 5

White blood cell subset profiles over time after multiple dose administration of mocravimod or placebo. Results are shown as mean (solid line) and 95% confidence interval (shaded area).