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ORIGINAL RESEARCH ARTICLE

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Axatilimab in Healthy Japanese Male Participants: Results from a Phase 1, Randomized, Double-Blind, Dose-Escalation Study

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Abstract

Background Axatilimab, an anti-colony-stimulating factor 1 receptor (CSF-1R) antibody, blocks colony-stimulating factor 1 (CSF-1) and interleukin-34 (IL-34) binding to CSF-1R on macrophages and monocytes. Axatilimab has demonstrated efficacy and safety in chronic graft-versus-host disease, and its safety, pharmacokinetics (PK), and pharmacodynamics (PD) were characterized in healthy Western participants.

Objective The objective of this study was to evaluate the safety, PK, and PD of axatilimab among healthy Japanese men.

Methods In this double-blind, randomized, dose-escalation study, eligible participants were healthy Japanese men aged 18–55 years, with a body weight of 50–100 kg, a body mass index of 18.0–30.0 kg/m^2, and no clinically significant findings on screening evaluation (clinical, laboratory, electrocardiogram, and physical exam). Participants were randomized to receive axatilimab or placebo in a 3:1 ratio in a blinded manner. Safety (30 d follow-up; primary endpoint), PK, and PD were evaluated at a clinic in Japan following single-dose infusions of axatilimab 0.3 mg/kg ($n = 6$), axatilimab 1.0 mg/kg ($n = 9$), or placebo ($n = 5$).

Results Three participants receiving axatilimab experienced a nonserious treatment-emergent adverse event (nasopharyngitis [0.3-mg/kg dose], amylase level increased [1.0-mg/kg dose], and headache [1.0-mg/kg dose]), with no clinically meaningful trends in hematology, urinalysis, physiologic, and most clinical chemistry measures. PK exposure increased with the 1.0 mg/kg versus 0.3 mg/kg dose, with greater than dose-proportional increases in area under the curve. CSF-1 and IL-34 levels had dose-dependent increases following axatilimab infusion. A transient increase in nonclassical monocytes was observed for 8 h following axatilimab infusion and then decreased below baseline until day 8 (0.3 mg/kg) or day 15 (1.0 mg/kg). The inverse effect was observed with classical monocytes. Intermediate monocytes had similar transient increases as nonclassical monocytes.

Conclusions A single dose of axatilimab 0.3 mg/kg and 1.0 mg/kg was generally well tolerated in healthy Japanese men. Safety, PK, and PD findings were consistent with those observed in healthy Western participants.

Trial Registration Japan Registry for Clinical Trials, jRCT2071220109; 27 February 2023.

1 Introduction

Chronic graft-versus-host disease (cGVHD) is a multiorgan immune-mediated complication that affects approximately half of patients receiving allogeneic hematopoietic stem cell transplantation [1–5]. Current therapies for cGVHD have limited effectiveness, with most patients developing disease that is refractory to first-line treatment

Key Points

Single-dose axatilimab (0.3 or 1.0 mg/kg) was generally well tolerated in healthy Japanese men.

Changes in cytokines and monocytes following axatilimab administration were consistent with the proposed mechanism of action for axatilimab.

Safety, tolerability, pharmacokinetics, and pharmacodynamics of axatilimab in healthy Japanese men were similar to the results observed in healthy Western participants.

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(typically systemic corticosteroids) and requiring ≥ 1 lines of subsequent therapy [3, 6, 7].

Colony-stimulating factor 1 receptor (CSF-1R) signaling-dependent monocytes and macrophages contribute to the multiorgan inflammation and fibrosis that drives cGVHD [8]. Axatilimab is a high-affinity humanized monoclonal antibody that blocks binding of colony-stimulating factor 1 (CSF-1) and interleukin-34 (IL-34) to CSF-1R [9], the key regulatory pathway determining the development of mononuclear phagocytic cells [10].

In a phase 1/2 study [9] (NCT03604692) and the pivotal phase 2 AGAVE-201 study [11] (NCT04710576) in patients with cGVHD, axatilimab demonstrated rapid and durable responses in all affected organs and patient subgroups, with significant reductions in symptom burden and a manageable safety profile. A detailed study of safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a single dose of axatilimab was previously conducted in healthy Western participants in the Netherlands [12]. The applicability of these results to Japanese patients remains unknown, necessitating further study to support a future clinical trial in Japanese patients with cGVHD. The present study reports the safety, tolerability, PK, and PD of two dose levels of axatilimab among healthy Japanese participants.

2 Methods

2.1 Participants and Study Design

This was a single-center, double-blind, randomized, placebo-controlled, dose-escalation phase 1 study (Japan Registry for Clinical Trials, jRCT2071220109). Eligible participants were healthy Japanese men aged 18–55 years, with a body weight of 50–100 kg, a body mass index (BMI) of 18.0–30.0 kg/m^2 (for comparability with the study in Western participants [12]), and no clinically significant findings on screening evaluation (clinical, laboratory, electrocardiogram [ECG], and physical exam; Fig. 1). Exclusion criteria included a history of clinically significant findings and recent use of medications (aside from occasional use of acetaminophen, ibuprofen, and vitamins).

Participants were randomized to receive axatilimab or placebo in a 3:1 ratio. A randomization list was generated by the sponsor before the start of the study according to a predefined algorithm using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) programming; participants were assigned to treatment groups using a block randomization method with a block size of four. Investigators and recruited participants were blinded, except for a pharmacist whose sole role in the study was to prepare the axatilimab or placebo infusion. Cohort 1 received a single intravenous (IV) infusion of axatilimab 0.3 mg/kg ($n = 6$) or placebo ($n = 2$). Following a safety review of ≥ 6 participants (≥ 4 of whom have received axatilimab) from cohort 1, cohort 2 received a single IV infusion of axatilimab 1.0 mg/kg ($n = 9$) or placebo ($n = 3$).

Participants were administered therapy on day 1 and were monitored in the clinical research unit until day 8. Participants returned for safety evaluations on days 15 and 22 and for a safety follow-up on day 30 (+3 days). Blood was sampled on days 1, 2, 3, 4, 8, 15, 22, and 30 for PK analyses. Blood samples were collected at regular intervals throughout for PD analyses.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and other applicable local regulations. Written informed consent/assent was provided by all participants prior to enrollment. Study protocols were approved by the SOUSEIKAI Hakata Clinic Institutional Review Board. This trial was registered with the Japan Registry for Clinical Trials (jRCT2071220109) on 27 February 2023.

2.2 Assessments

The primary endpoint was the frequency and severity of treatment-emergent adverse events (TEAEs), assessed by physical examination, vital signs, 12-lead ECG, and clinical laboratory data. TEAEs were coded using Medical Dictionary for Regulatory Activities version 25.1. The secondary endpoint was PK parameters, assessed with a standard noncompartmental analysis method using Phoenix® WinNonlin version 8.3.4 (Certara USA, Princeton, New Jersey, USA). Plasma samples were analyzed for axatilimab using a sandwich enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation of 150 ng/mL and an upper limit of quantitation of 10,000 ng/mL.

Exploratory PD endpoints included change from baseline in CSF-1 and IL-34 levels, assessed by commercially available ELISAs (R&D Systems, Minneapolis, Minnesota, USA; Human M-CSF and Human IL-34 Quantikine ELISA Kits), and change from baseline in circulating monocyte numbers (cluster of differentiation [CD]14/CD16), assessed by flow cytometry. Monocyte subsets were characterized as nonclassical (CD14^{low}/CD16^{high}), classical (CD14^{high}/CD16^{low}), or intermediate (CD14^{high}/CD16^{high}) and quantified as a proportion of the total monocyte population (represented by the CD14+ human leukocyte antigen–DR isotype positive [HLA-DR+] subset of CD45+ immune cells). Immunogenicity was assessed by detection of anti-axatilimab antibodies in the plasma using an electrochemiluminescent assay with a sensitivity of 6.70 ng/mL.

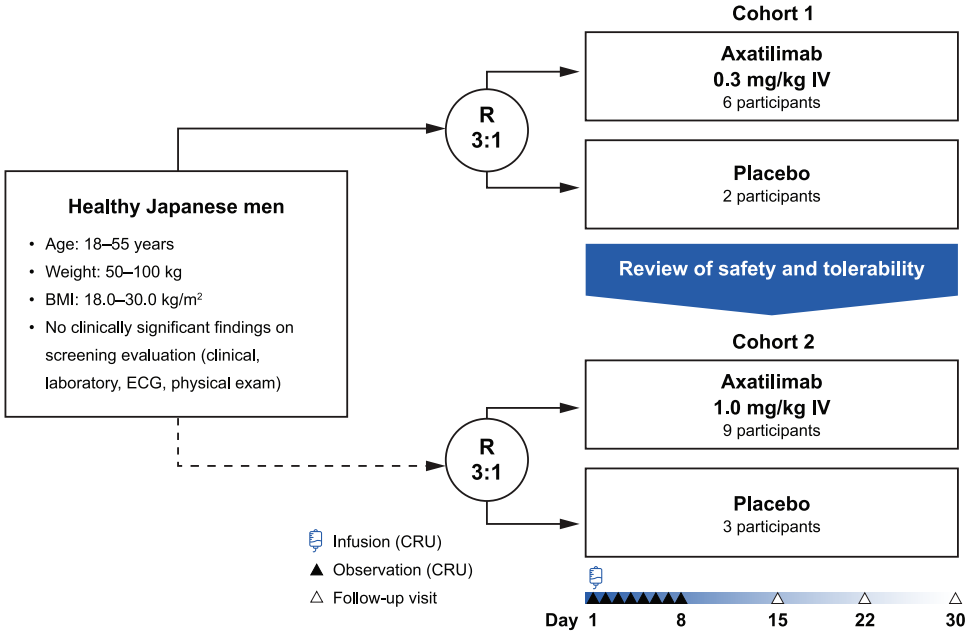

Fig. 1 Study design. BMI, body mass index; CRU, clinical research unit; ECG, electrocardiogram; IV, intravenous; R, randomization

2.3 Statistical Analyses

TEAEs, ECGs, vital signs, and clinical laboratory tests were summarized with descriptive statistics. For PK analyses, dose proportionality of axatilimab was assessed using an analysis of variance on dose-normalized, natural logarithmic-transformed PK parameters (maximum plasma concentration [C_{max}], area under the curve from time 0 to the last measurable timepoint [AUC_{0-t}], and area under the curve from time 0 to infinity [AUC_{0-inf}]) using the 90% CIs around the geometric mean ratios of PK parameters for the 0.3-mg/kg dose in comparison with the reference dose of 1.0 mg/kg. The statistical significance of the median treatment difference in time to maximum concentration was examined using the Kruskal–Wallis test and the Hodges–Lehmann method. For PD analyses, data from the participants receiving placebo in both cohorts were combined, and all data were analyzed using GraphPad Prism version 9.3.1 (GraphPad Software, Boston, Massachusetts, USA).

3 Results

3.1 Participants

A total of 20 participants were enrolled and completed the study between 15 and 23 March 2023. All participants were Japanese men aged 19–51 years with a mean (SD) BMI of 22.4 (2.2) kg/m^2. Details by cohort are provided in Table 1. All 20 participants were included in the safety population and PD analyses, and the 15 participants treated with axatilimab were included in PK and immunogenicity analyses.

3.2 Safety

A total of three participants who received axatilimab experienced TEAEs during the study (Table 2). One participant receiving the 0.3-mg/kg dose of axatilimab (cohort 1) experienced nasopharyngitis (grade 2), which was not considered by the investigator as related to the study drug. One participant receiving axatilimab 1.0 mg/kg (cohort 2) had an increase in amylase levels (grade 1), and another participant who received the 1.0-mg/kg dose (cohort 2) experienced a headache (grade 1); both events were considered by the investigator as related to the study drug. All TEAEs resolved by the end of the study. There were no serious or fatal TEAEs.

There were no clinically meaningful trends in hematology, urinalysis, mean vital signs, body weight, mean 12-lead ECG, and most clinical chemistry measures. Most clinical chemistry abnormalities were grade 0–2. An increase in mean amylase levels of approximately 30% from baseline was noted starting at day 4 in participants who received axatilimab 1.0 mg/kg (cohort 2) only, and these increases resolved by day 22 without treatment. A grade 3 increase in cholesterol emerged in ≥ 1 postbaseline timepoint for one participant treated with axatilimab 0.3 mg/kg (cohort 1) and one participant treated with axatilimab 1.0 mg/kg (cohort 2). A grade 3 increase in sodium occurred in one participant treated with axatilimab 0.3 mg/kg (cohort 1).

Table 1 Patient demographics and baseline clinical characteristics

Characteristic	Cohort 1		Cohort 2	
	Axatilimab 0.3 mg/kg ($n = 6$)	Placebo 0.3 mg/kg ($n = 2$)	Axatilimab 1.0 mg/kg ($n = 9$)	Placebo 1.0 mg/kg ($n = 3$)
Age, mean (SD), years	27.5 (12.4)	20.5 (0.7)	35.0 (11.0)	36.0 (12.3)
Male, *n* (%)	6 (100)	2 (100)	9 (100)	3 (100)
Asian, *n* (%)	6 (100)	2 (100)	9 (100)	3 (100)
Weight, mean (SD), kg	65.4 (4.7)	74.0 (0.3)	65.4 (7.2)	64.0 (4.3)
BMI, mean (SD), kg/m^2	22.3 (1.9)	24.4 (1.8)	22.2 (2.8)	22.0 (0.7)

BMI, body mass index; SD, standard deviation

3.3 PK

The axatilimab plasma concentration–time profile is shown in Fig. 2. Axatilimab exposure increased with the 1.0-mg/kg dose (cohort 2) compared with the 0.3-mg/kg dose (cohort 1; Table 3). Geometric mean values for C_{max} increased from 5.7 to 21.5 µg/mL in a dose-proportional manner. Geometric mean values for AUC_{0-t} increased from 134 to 1460 h µg/mL and AUC_{0-inf} increased from 151 to 1620 h µg/mL; both increases occurred in a greater than dose-proportional manner ($P < 0.0001$). Geometric mean values for half-life increased from 21.1 to 53.2 h. Correspondingly, geometric mean values for clearance (CL) and volume of distribution were lower with the 1.0-mg/kg dose of axatilimab (cohort 2) compared with the 0.3-mg/kg dose (cohort 1). CL decreased from 0.130 to 0.040 L/h. Apparent volume of distribution during the terminal phase decreased from 3.96 to 3.07 L. Steady-state volume of distribution decreased from 3.94 to 3.16 L.

3.4 Immunogenicity

Among all 15 participants treated with axatilimab, none had detectable anti-axatilimab antibodies at baseline. One participant who received the 0.3-mg/kg dose (cohort 1) developed anti-axatilimab antibodies after treatment, but PK parameters were unaffected.

3.5 PD

CSF-1 and IL-34 levels increased in a dose-dependent manner following infusion of axatilimab (Fig. 3). Both remained below the limit of detection in participants who received placebo.

Among participants who received axatilimab, the number of nonclassical monocytes transiently increased, peaking at 4 h after infusion and remaining above baseline at 8 h after infusion (Fig. 4A). Nonclassical monocytes subsequently decreased below the detection limit by day 3, recovering to baseline by day 8 (axatilimab 0.3 mg/kg, cohort 1) or day 15

Table 2 Summary of treatment-emergent adverse events

n (%)	Cohort 1		Cohort 2	
	Axatilimab 0.3 mg/kg ($n = 6$)	Placebo 0.3 mg/kg ($n = 2$)	Axatilimab 1.0 mg/kg ($n = 9$)	Placebo 1.0 mg/kg ($n = 3$)
Participants with a TEAE[a]	1 (16.7)	0	2 (22.2)	0
Amylase increased (grade 1)	0	0	1 (11.1)	0
Headache (grade 1)	0	0	1 (11.1)	0
Nasopharyngitis (grade 2)	1 (16.7)	0	0	0
Participants with a treatment-related TEAE	0	0	2 (22.2)	0
Amylase increased	0	0	1 (11.1)	0
Headache	0	0	1 (11.1)	0
Participants with a TEAE leading to discontinuation	0	0	0	0
Participants with a grade ≥ 3 TEAE	0	0	0	0
Participants with a fatal TEAE	0	0	0	0

TEAE, treatment-emergent adverse event

[a]All TEAEs resolved

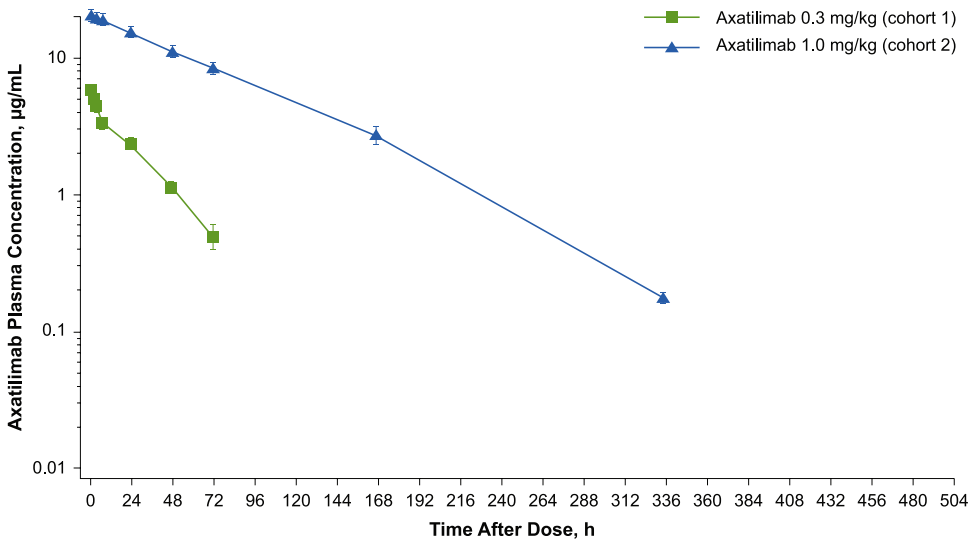

Fig. 2 Axatilimab plasma concentration-time profile. Data are shown on a semi-logarithmic scale

Table 3 Summary of pharmacokinetic parameters for axatilimab

Parameter	Cohort 1 Axatilimab 0.3 mg/kg ($n = 6$)	Cohort 2 Axatilimab 1.0 mg/kg ($n = 9$)
C_{max}, µg/mL	5.7 (14)	21.5 (13)
t_{max}, h	0.5 (0.5–2.0)	2.0 (0.5–8.0)
AUC_{0-t}, h µg/mL	134 (14)	1460 (24)
AUC_{0-inf}, h µg/mL	151 (17)	1620 (26)
$t_{1/2}$, h	21.1 (29)	53.2 (23)
CL, L/h	0.130 (20)	0.040 (18)
V_z, L	3.96 (12)	3.07 (19)
V_{ss}, L	3.94 (10)	3.16 (14)

Data are presented as geometric mean (coefficient of variation, %), except for t_{max} (median [range])

AUC_{0-t}, area under the curve from time 0 to the last measurable timepoint; AUC_{0-inf}, area under the curve from time 0 to infinity; CL, clearance; C_{max}, maximum concentration; $t_{1/2}$, half-life; t_{max}, time to maximum concentration; V_{ss}, steady-state volume of distribution; V_z, apparent volume of distribution during the terminal phase

(axatilimab 1.0 mg/kg, cohort 2). No changes in nonclassical monocytes were observed for participants receiving placebo.

The inverse effect on classical monocytes relative to nonclassical monocytes was observed in response to axatilimab (Fig. 4B). A transient decrease occurred, reaching a minimum at 4 h after infusion, and remaining below baseline until 8 h after infusion. Levels increased above baseline by day 3 and remained elevated at day 4, before returning to baseline by day 8 (axatilimab 0.3 mg/kg, cohort 1) or day 15 (axatilimab 1.0 mg/kg, cohort 2). No changes in classical monocytes were observed for participants receiving placebo.

Intermediate monocytes had a similar transient increase as nonclassical monocytes (Fig. 4C). Levels then returned to baseline and were similar to the levels observed with the placebo cohort. There were no significant differences in total monocyte counts between cohorts (data not shown).

4 Discussion

This article reports the first study of axatilimab, an anti-CSF-1R monoclonal antibody, in Japanese individuals. Single-dose axatilimab (0.3 mg/kg [cohort 1] or 1.0 mg/kg [cohort 2]) was generally well tolerated in healthy Japanese men, with no grade ≥ 3 TEAEs and no notable trends or treatment-emergent safety concerns observed from clinical laboratory tests, vital signs, or 12-lead ECGs.

Axatilimab exposure (AUC_{0-t} and AUC_{0-inf}) with the 0.3- and 1.0-mg/kg doses (cohorts 1 and 2, respectively) increased in a more than dose-proportional manner, suggesting nonlinear PK, whereas C_{max} increased in a dose-proportional manner. Other PK parameters changed as expected with an increased dose. Of the 15 participants who received axatilimab, 1 participant who received the 0.3-mg/kg dose (cohort 1) was positive for anti-axatilimab antibodies. Nonetheless, PK parameters from this participant suggested that the presence of anti-axatilimab antibodies did not impact the PK of axatilimab at the 0.3-mg/kg dose level.

Following axatilimab infusion with either dose, circulating CSF-1 and IL-34 levels were increased, suggesting reduced ligand binding to CSF-1R. Following a transient increase, circulating nonclassical monocytes decreased in a dose- and time-dependent manner, with a corresponding increase in classical monocytes. This is consistent with axatilimab inhibition of CSF-1R, a receptor that promotes the differentiation and infiltration of

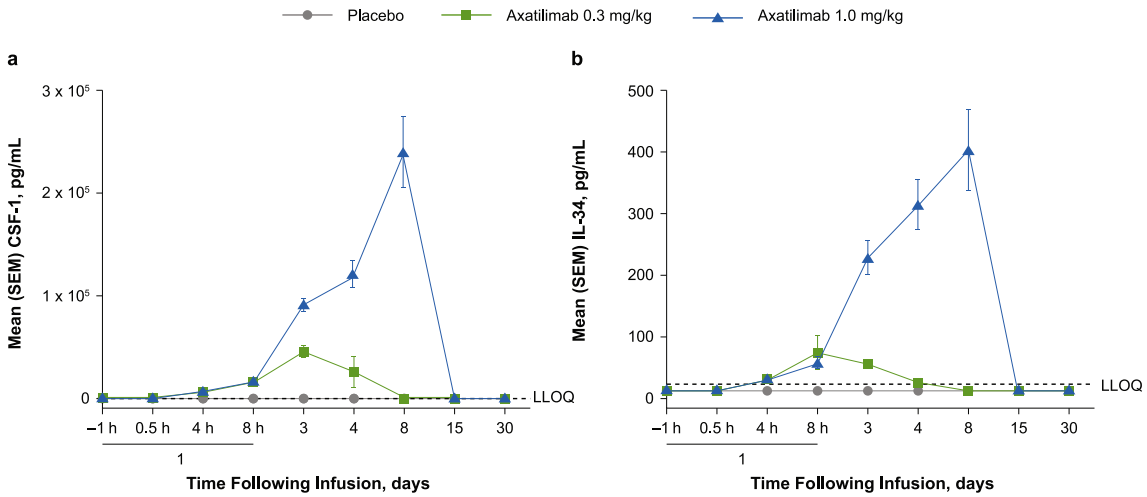

Fig. 3 CSF-1 (a) and IL-34 (b) levels following axatilimab infusion. CSF-1, colony-stimulating factor 1; IL-34, interleukin-34; LLOQ, lower limit of quantification

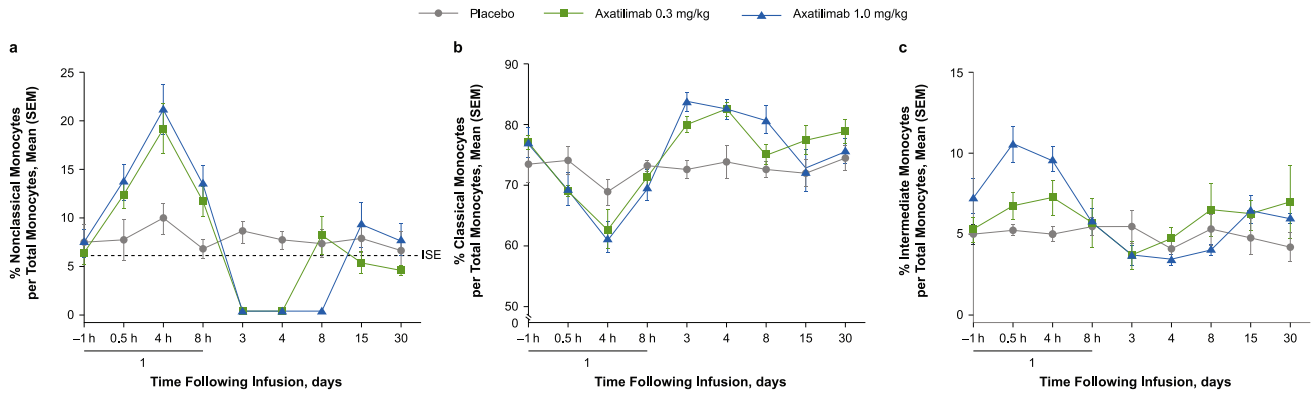

Fig. 4 Nonclassical ($CD14^{low}/CD16^{high}$, a), classical ($CD14^{high}/CD16^{low}$, b), and intermediate ($CD14^{high}/CD16^{high}$, c) monocyte subsets following axatilimab infusion. CD, cluster of differentiation; ISE, insufficient events

nonclassical monocytes from circulation into tissue [8, 13]. Although nonclassical monocytes can have antiinflammatory functions, evidence suggests they may contribute to the pathogenesis of chronic inflammatory diseases, including cGVHD [14–16]. Differentiated macrophages, which are CSF-1R dependent, contribute to epidermal inflammation and subcutaneous and cutaneous fibrosis in cGVHD through production of transforming growth factor-β [8, 17]. The cause and source of the transient increase in nonclassical monocytes in the circulation that precedes the major reduction remain to be determined.

A previous study in healthy Western participants found that doses ≤ 1.0 mg/kg were well tolerated, with the most frequent complaint being mild-to-moderate itching that lasted 2 or 3 days [12]. Axatilimab was also well tolerated in cohort 1 (0.3 mg/kg dose) and cohort 2 (1.0 mg/kg dose) of the present study. With the 1.0-mg/kg dose, the maximum levels of CSF-1 and IL-34 reached in the present study were comparable to the levels observed in healthy Western participants [12]. The study in healthy Western participants also detected a reduction in nonclassical monocytes and greater than dose-proportional increases in area under the curve [12]. Our findings were consistent with these results.

A limitation of the study was the small sample size, which is typical in phase 1 studies. Small sample size may have contributed to a slight discordance among baseline characteristics (weight, BMI) between treatment groups in cohort 1 due to random variation, but these differences were not expected to significantly impact the overall study conclusions. Although the inclusion of only men in this study may limit the generalizability of its study, there are no data suggesting that findings would differ in women. Men were exclusively recruited to minimize potential for variability (e.g., due to hormone fluctuations, fat distribution) and safety risks (e.g., in women with childbearing potential) in this early study; this approach was able to minimize the

number of participants while confirming whether the effects of axatilimab in Japanese participants were consistent with those observed in a similar study of Western participants. Characterization of sex differences among different ethnicities may occur as the clinical program progresses. Further evaluation of the efficacy and safety of axatilimab in Japanese patients with cGVHD is warranted. On the basis of these results, a study to evaluate the efficacy and safety of axatilimab in patients with recurrent or refractory cGVHD has been initiated (NCT06263478).

5 Conclusions

Taken together, these results demonstrate that a single dose of axatilimab is well tolerated and does not present safety concerns at the 0.3- and 1.0-mg/kg dose levels in healthy Japanese men. Furthermore, axatilimab appears to function in accordance with the previously proposed mechanism of action. Safety, PK, and PD findings in healthy Japanese participants were consistent with those from healthy Western participants.

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Declarations

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Conflict of interest M.H. is an employee of SOSEIKAI Hakata Clinic. K.K. and K.S. are employees of Incyte Biosciences Japan GK and shareholders of Incyte Corporation. Y.Y., H.L., and M.P. are employees and shareholders of Incyte Corporation.

Availability of data and material Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after 1 January 2020 in ≥ 1 major market (e.g., USA, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

Ethics approval The study was conducted in accordance with the provisions of the 1964 Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice, and other applicable local regulations. Study protocols were approved by the SOUSEIKAI Hakata Clinic Institutional Review Board (approval no. VV-TMF-228501) on 9 February 2023.

Consent to participate Written informed consent/assent was provided by all participants prior to enrollment.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions All authors contributed to study conception and design, data collection, data analysis, manuscript preparation, and commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

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