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ORIGINAL RESEARCH

Long-term safety and efficacy of anti-TNF multivalent VHH antibodies ozoralizumab in patients with rheumatoid arthritis

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ABSTRACT

Objectives This study aimed to evaluate the long-term safety and efficacy profiles of ozoralizumab in patients with rheumatoid arthritis (RA) from the OHZORA, NATSUZORA and HOSHIZORA trials.

Methods This study conducted an integrated analysis of the three trials. Patients who completed the OHZORA trial with concomitant treatment of ozoralizumab and methotrexate (MTX) or the NATSUZORA trial without MTX were eligible to participate in the long-term extension HOSHIZORA trial. Safety assessment was performed in the safety analysis set, and the incidence rate per 100 person-year (PY) was calculated for a summary of adverse events (AEs) and AEs of special interests (AESIs). The efficacy was analysed in terms of disease activity index response rates and functional remission.

Results The OHZORA and NATSUZORA trials enrolled 521 patients, of whom 401 patients entered the HOSHIZORA trial and 279 completed the long-term extension treatment with a mean treatment duration of 200 weeks and total exposure of 1419.34 PY in all enrolled patients. Of the patients, 96.9% demonstrated ≥1 AEs, which is mostly mild to moderate. One death was observed, but no conspicuous AEs emerged and no specific concerns in AESIs were found through the long-term administration. The efficacy assessment revealed the maintained American College of Rheumatology response rates of 20%, 50%, and 70% during the trials.

Conclusion This integrated analysis revealed no new safety concerns, and the efficacy was maintained in patients with RA under long-term ozoralizumab administration.

Trial registration number jRCT2080223971, jRCT2080223973, NCT04077567.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ozoralizumab, a next-generation antitumour necrosis factor variable heavy-chain domains of heavy-chain antibody, demonstrated its efficacy and safety in patients with rheumatoid arthritis (RA) for 52 weeks with and without methotrexate; however, the long-term profile of ozoralizumab was not reported.

WHAT THIS STUDY ADDS

⇒ This integrated analysis provided evidence indicating no specific safety concerns and the maintained efficacy in patients with RA under long-term ozoralizumab treatment with a mean duration of 200 weeks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This report indicates ozoralizumab as a new RA treatment option for the long-term use of biological disease-modifying antirheumatic drugs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by cartilage destruction and joint damage.[1] In the last two decades, RA treatment has improved, with the emergence of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs. Tumour necrosis factor inhibitors (TNFis) were developed as the first bDMARDs, and six TNFis are available in Japan as of this report.

Ozoralizumab is a 38 kDa next-generation anti-TNF antibody composed of two humanised antihuman TNF variable heavy-chain domains of heavy-chain antibodies (VHH) and one humanised antihuman serum albumin (HSA) VHH. VHH antibodies are derived from a special type of heavy-chain-only antibody that llamas and other camelid species naturally produce.[2 3] Ozoralizumab demonstrated an inhibitory activity against human TNF and a specific binding ability to HSA, which caused potent TNF action neutralisation and prolonged serum half-life by interacting with serum albumin.[4–8] Additionally, a non-clinical study in mice revealed that ozoralizumab exhibited quick

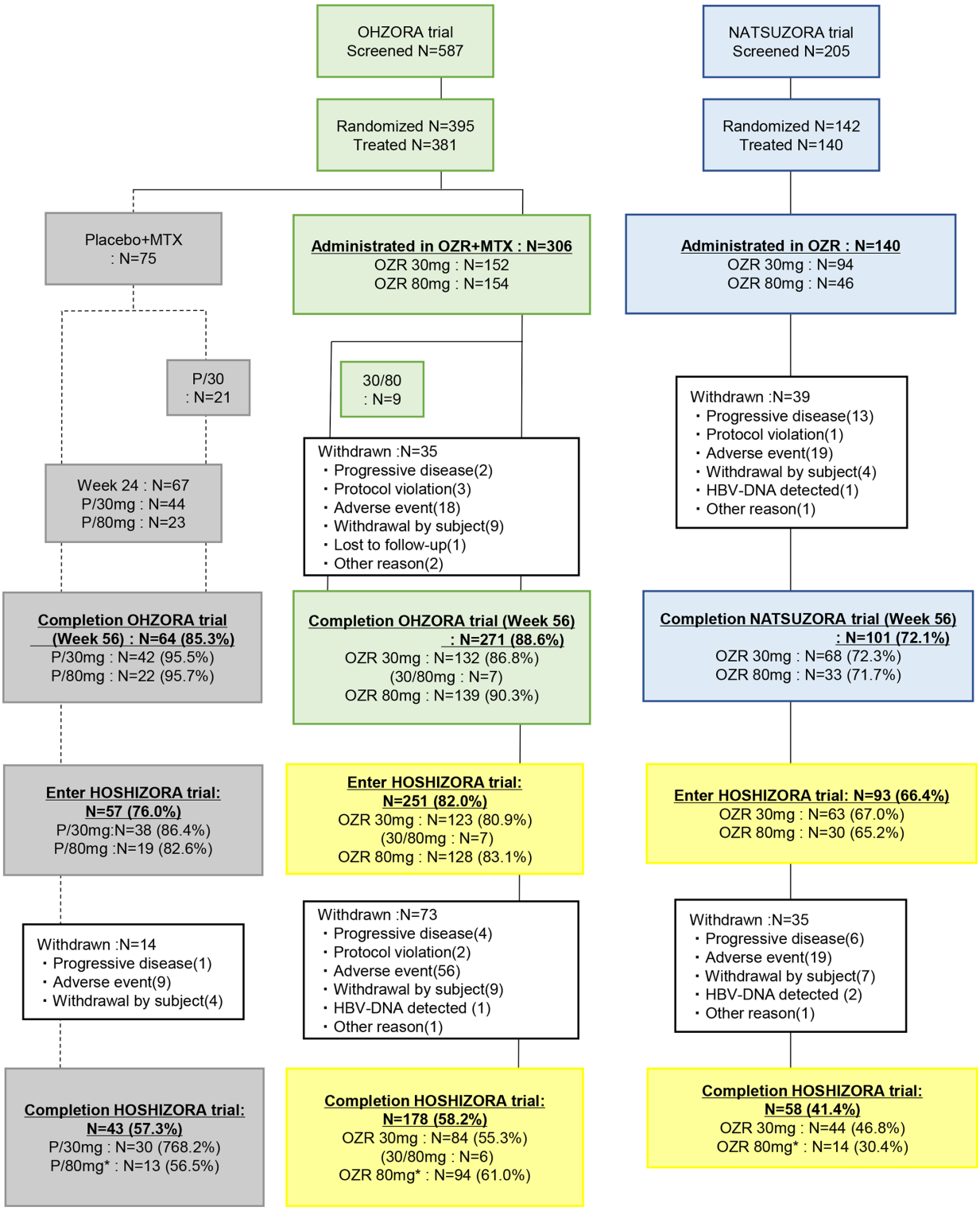

Figure 1 Patient disposition, including OHZORA, NATSUZORA trials, and subsequent long-term extension HOSHIZORA trial. P/30, P/80 and 30/80 indicate the groups of patients who were originally randomised to placebo (P) or 30 mg (30) of ozoralizumab at the start of the OHZORA trial and changed to 30 mg or 80 mg (80) of ozoralizumab at week 20 due to meeting the criteria for early escape. LTE, long-term extension; MTX, methotrexate; OZR, ozoralizumab. *Dose changed from 80 mg to 30 mg after approval submission.

biodistribution to inflammatory tissue and inflammatory response reduction by immune complex with TNF due to its unique structure of small molecular weight and lack of Fc region.[9 10]

The efficacy and safety of ozoralizumab were previously reported in patients with active RA with methotrexate (MTX) in the OHZORA trial[11 12] and without MTX in the NATSUZORA trial,[13] followed by the long-term

Table 1 Demographic and other baseline characteristics for SAF

	30 mg (n=290)	Total (n=513)
Sex, female, no. (%)	211 (72.8)	390 (76.0)
Age, years	55.8±11.9	55.8±11.6
Age <65 years, no. (%)	209 (72.1)	371 (72.3)
Weight, kg	59.22±13.28	58.95±12.92
Disease duration, years	7.2±7.1	7.6±7.5
Concomitant MTX, no. (%)	196 (67.6)	373 (72.7)
Concomitant csDMARDs except for MTX, no. (%)	51 (17.6)	72 (14.0)
Corticosteroid use, no. (%)	133 (45.9)	228 (44.4)

Demographic and other baseline characteristics at the start of the trials for SAF.
csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; MTX, methotrexate; SAF, safety analysis set.

extension HOSHIZORA trial. Ozoralizumab demonstrated the treatment advantages in these trials derived from its molecular features described above. Rapid improvement of disease activity was observed at day 3 in OHZORA trial,[11] which was unique data of ozoralizumab not existing with other TNFis. Sustained efficacy during the dosing interval extension from 4 weeks to 8 weeks was demonstrated in the HOSHIZORA trial.[14]

RA is a chronic disease that requires long-term intervention; thus, demonstrating a good long-term profile is significant for RA treatment. Here, we report the long-term safety and efficacy of ozoralizumab through integrated analysis of the OHZORA, NATSUZORA and HOSHIZORA trials.

METHODS

Patients

Inclusion and exclusion criteria for the OHZORA and NATSUZORA trials were previously described.[11–13] Patients who completed either trial and provided informed consent were eligible for the HOSHIZORA trial. The key exclusion criteria for the HOSHIZORA trial were patients who had serious adverse drug reactions in the previous trials and those who had not recovered from clinically important adverse events (AEs).

Trial design

Trial designs for the OHZORA and NATSUZORA trials were previously described.[11–13] The HOSHIZORA trial was an open-label, multicentre, long-term extension trial conducted from October 2019 to June 2023 at 77 sites in Japan (NCT04077567). Patients who participated in the HOSHIZORA trial received ozoralizumab of 30 mg or 80 mg subcutaneously every 4 weeks, a similar dose to previous trials. Patients who received 80 mg of treatment changed their dose to 30 mg after determining the approval submission dose of 30 mg. Ozoralizumab received market approval in Japan with the indication of RA in September 2022. Patients could be administered conventional synthetic DMARDs (csDMARDs), including MTX, within the dose of previous trials and dose change, and permanent or temporary discontinuation of concomitant csDMARDs was permitted. Patients who received 30 mg of treatment and achieved low disease activity (Disease Activity Score in 28 joints (DAS28) with erythrocyte sedimentation rate <3.2) at two consecutive time points could extend the dosing interval to 8 weeks at the investigator's discretion. We reported the efficacy and safety of ozoralizumab under 8 weeks of interval treatment.[14]

Safety

Safety data, including AEs, adverse drug reactions (ADRs) and AE of special interest (AESI), were summarised by the number of patients and incidence rate (IR). AESIs were identified according to the Japanese version of the Medical Dictionary for Regulatory Activities (V.22.1).

Efficacy

Efficacy end points included the American College of Rheumatology (ACR)20/50/70 response rate, Simplified (SDAI) and Clinical (CDAI) Disease Activity Index, DAS28 based on C reactive protein (CRP), Boolean remission and Health Assessment Questionnaire Disability Index (HAQ-DI). The proportion of patients achieving remission and low-disease (LDA), middle-disease and high-disease activity was assessed based on SDAI of ≤3.3, >3.3–11.0, >11.0–26.0 and >26.0, CDAI of ≤2.8, >2.8–10.0, >10.0–22.0 and >22.0, DAS28-CRP of <2.6, ≥2.6–<3.2, ≥3.2–5.1 and >5.1, respectively, and functional remission of HAQ-DI of ≤0.5.

Statistical analysis

Safety was assessed using the safety analysis set (SAF), defining patients who were administered ozoralizumab and received safety measurement or observation at least a time through the trials. IR was calculated as the number of events per 100 person-year (PY) with a 95% CI.

Efficacy was assessed in the full analysis set (FAS), defining patients who were randomised to the ozoralizumab treatment group at the start of the previous trials and performed efficacy measurements at least a time after initiating ozoralizumab treatment. Basic statistics were calculated by the observed case (OC) and the response rate was calculated by non-responder imputation (NRI). No statistical hypothesis testing was performed.

Safety and efficacy assessments defined two treatment groups: the 30 mg group, consisting of patients randomised to 30 mg of ozoralizumab at the start of the previous trials and the total group, which included all participants, including the 30 mg group.

The 30 mg group was defined as the patients who were administered 30 mg for the first ozoralizumab dose in safety assessments. Patients who changed their dose from 30 mg to 80 mg were excluded from safety assessments in the 30 mg group after dose change. For the efficacy evaluation, the 30 mg group was defined as patients

Table 2 Overview of AEs and ADRs

		30 mg		Total	
		773.39		1419.34	
Total exposure (PY)		AE	ADR	AE	ADR
Total events	No. (%)	278 (95.9)	164 (56.6)	497 (96.9)	292 (56.9)
	IR	336.18	69.56	336.71	63.34
	95% CI	(323.51 to 349.36)	(63.93 to 75.70)	(327.29 to 346.39)	(59.33 to 67.62)
Severity					
Mild	No. (%)	267 (92.1)	129 (44.5)	482 (94.0)	232 (45.2)
	IR	278.77	54.18	277.10	48.54
	95% CI	(267.25 to 290.79)	(49.23 to 59.62)	(268.57 to 285.90)	(45.05 to 52.31)
Moderate	No. (%)	128 (44.1)	53 (18.3)	246 (48.0)	99 (19.3)
	IR	52.37	13.58	54.60	13.03
	95% CI	(47.51 to 57.72)	(11.21 to 16.44)	(50.89 to 58.59)	(11.29 to 15.05)
Severe	No. (%)	31 (10.7)	14 (4.8)	57 (11.1)	24 (4.7)
	IR	5.04	1.81	5.00	1.76
	95% CI	(3.68 to 6.90)	(1.07 to 3.06)	(3.96 to 6.31)	(1.19 to 2.61)
Leading to death	No. (%)	–	–	1 (0.2)	1 (0.2)
	IR	–	–	0.70	0.49
	95% CI	–	–	(0.38 to 1.31)	(0.24 to 1.03)
Other serious AEs except death	No. (%)	55 (19.0)	20 (6.9)	101 (19.7)	32 (6.2)
	IR	9.31	2.84	8.95	2.47
	95% CI	(7.39 to 11.73)	(1.87 to 4.32)	(7.52 to 10.65)	(1.77 to 3.43)
Leading to discontinuation	No. (%)	68 (23.4)	32 (11.0)	126 (24.6)	56 (10.9)
	IR	9.05	4.40	9.30	4.16
	95% CI	(7.16 to 11.44)	(3.14 to 6.15)	(7.84 to 11.03)	(3.22 to 5.37)

Each item consists of the number of subjects (%), IR per 100 PY and 95% CI. Severity was categorised with one subject in each category: mild, moderate and severe.
ADR, adverse drug reaction; AE, adverse event; IR, incidence rate; PY, person-year.

randomised to 30 mg ozoralizumab at the start of the previous trials. The total group in both safety and efficacy was defined as those participating in the trials, including the 30 mg group.

RESULTS

Patient disposition

The OHZORA and NATSUZORA trials initiated ozoralizumab or placebo administration in 521 patients and the HOSHIZORA trial in 401 patients (77.0%) (figure 1). Of them, 370 (71.0%) and 323 (62.0%) patients continued the trial at weeks 104 and 156, respectively, and finally 279 (53.6%) patients completed the HOSHIZORA trial (completion rate: 279/401, 69.6%). The mean duration of treatment was 200 weeks (minimum–maximum=130–228 weeks) among the completers of the HOSHIZORA trial. A total of 242 (46.4%) patients were either not enrolled in the HOSHIZORA trial due to inclusion/exclusion criteria or discontinued from the trials. The most frequent reason for discontinuation throughout the trials was AEs, including COVID-19 infection in 36 patients. Withdrawal by subject and progressive disease were subsequent reasons for discontinuation, as shown in figure 1. Online supplemental table 1 shows the trial continuous rate depending on the previous trials.

Demographics and patient characteristics

Table 1 shows patient demographics and baseline characteristics for SAF.

Female and male patients were included (72.8% and 76.0% in the 30 mg group and total group, respectively), with a mean (SD) age of 55.8 (11.9) and 55.8 (11.6) years, and a mean duration of disease of 7.2 (7.1) and 7.6 (7.5) years. Online supplemental table 2 shows demographics and patient characteristics for FAS.

Safety

Table 2 summarises AEs and ADRs.

Total exposures (PY) were 773.39 and 1419.34 in the 30 mg and total groups, respectively. Most of the AEs were mild and moderate. The only AE causing death throughout the total treatment period was observed

in a patient in whom disseminated tuberculosis has developed.[12]

Table 3 shows the list of AESIs and the occurrence of those events.

The most frequently emerging AESI was abnormal liver function tests, most of which were abnomal clinical laboratory test and were mostly mild in severity. 103 of 117 patients were concomitant with MTX. Serious infections, except for tuberculosis, were observed with incidence rates of 3.88 and 3.80 in the 30 mg and total groups, respectively. The trend in the type of infections was consistent with the OHZORA and NATSUZORA trials. Tuberculosis was observed in a patient administered with ozoralizumab of 80 mg in the OHZORA trial, causing death as mentioned above. The patient showed negative T-SPOT and no abnormal findings on chest X-rays at screening but developed tuberculosis on day 82 and died on day 105. However, no case of tuberculosis appeared thereafter, and the IR was 0.07 in the total group. Malignant tumours were observed with IRs of 2.33 and 1.76 in the 30 mg and total groups, respectively. The number of events of malignant tumours was 25, including 1 case of bladder cancer, gastric cancer, ovarian cancer, squamous cell carcinoma of lung, T-cell type acute leukaemia and tongue neoplasm malignant stage unspecified, 2 cases of lung adenocarcinomas and uterine cancers, 3 cases of breast cancers and diffuse large B-cell lymphomas, 4 cases of prostate cancers and 5 cases of colon cancers. The IR during the overall period revealed malignant tumours at a higher rate in the early treatment period. Thereafter, the IR gradually decreased and became steady, except for the last period after 48 months with small total exposure (online supplemental figure 1). Interstitial lung diseases were observed with IRs of 1.94 and 1.69 in the 30 mg and total groups, respectively, and higher rates appeared in the early treatment period, as well as malignant tumour. Major adverse cardiovascular events were observed with IRs of 0.39 and 0.28 in the 30 mg and total groups, respectively. No venous thromboembolisms were observed throughout the trials. Psoriasis was observed with an IR of 0.78 in both the 30 mg and total groups. Injection site reactions were observed with IRs of 9.70 and 5.99 in the 30 mg and total groups, respectively. Two patients from the OHZORA and NATSUZORA trials repeatedly manifested those reactions, Injection site pain was observed 42 times in one patient, who had an increased level of existing anti-ozoralizumab response and tested negative for neutralising antibody (NAb). Injection site swelling was observed 27 times in another patient, who also had an increased level of existing anti-ozoralizumab response and tested positive for NAb. Neither of these patients discontinued treatment due to injection site reactions.

These observations revealed no safety concerns under the long-term ozoralizumab administration.

Efficacy

Figure 2 shows the results of ACR20/50/70. These end points improved after the treatment initiation and were maintained throughout the trials. Final ACR20/50/70 responses at week 156 in NRI analysis were 43.1%/41.1%/34.1% and 44.8%/41.3%/33.4% in the 30 mg and total groups, respectively. Additionally, response rates in other efficacy end points demonstrated similar patterns (figure 3). Remission rates at week 156 in the 30 mg and total groups were 24.4% and 25.6% (SDAI), 23.2% and 24.7% (CDAI), 38.6% and 39.2% (DAS28-CRP), 21.1% and 20.9% (Boolean) and 38.6% and 38.6% (HAQ-DI), respectively. Response rates of efficacy end points in OC (online supplemental table 3) and ACR20/50/70 depending on the previous trials (online supplemental table 4) are shown in the online supplemental information. Throughout the trials, about 90% of patients in OC achieved remission or low disease activity. Online supplemental table 5 shows the subgroup analysis at week 156. Online supplemental table 6 shows the efficacy results in the HOSHIZORA trial for 104 weeks, as well as the completion and efficacy rates in extended dosing intervals for 56 weeks.

DISCUSSION

This integrated analysis of three trials with a mean treatment duration of 200 weeks and total exposure of 1419.34 PY in the total group presented the long-term profile of safety and efficacy for ozoralizumab in patients with RA.

The OHZORA, NATSUZORA and HOSHIZORA trials were conducted during pandemic of SARS-CoV-2[15] and were much affected. A total of 36 patients withdrew from the HOSHIZORA trial because of COVID-19 as AE, indicating an equivalent of approximately 10% of enrolled patients in the trial. However, the completion rate of the long-term use of ozoralizumab in this analysis was comparable with other TNFis.[16–22] Noteworthy, ozoralizumab possessed good treatment continuity itself.

In the overall safety profile, no AE had been newly observed or increased in the long-term administration with a maximum of 228 weeks in this integrated analysis, referring to the previous reports.[11–13] The trend of whole AE occurrence was the same level, and most AESIs demonstrated the same or lower extent of IRs compared with other TNFis reported from postmarketing surveillance or clinical trials in Japanese patients.[21–25]

Previous cohort studies reported malignant tumours and interstitial lung disease in patients with RA with TNFi treatment, with IRs of 0.60–0.74 and 0.16–0.87 per 100 PY, respectively.[26–31] This integrated analysis observed malignant tumours and interstitial lung disease with IRs of 1.76 and 1.69, respectively, in the total group, considering that this analysis was not a cohort study and had a small sample size with only the Japanese population. The post hoc analysis revealed a high IR for malignant tumours in the early stages of the trials, which gradually decreased and stabilised by the middle to end stages (online supplemental figure 1). Notably, malignancy screening by CT added to regular screening before treatment of bDMARDs or targeted synthetic DMARDs achieved a low IR in the early

Table 3 Summary of adverse events of special interest

		30 mg	Total
Total exposure (PY)		**773.39**	**1419.34**
Serious infection (except tuberculosis)	No. (%)	25 (8.6)	48 (9.4)
	IR	3.88	3.80
	95% CI	(2.71 to 5.55)	(2.91 to 4.97)
Tuberculosis	No. (%)	–	1 (0.2)
	IR	–	0.07
	95% CI	–	(0.01 to 0.50)
Interstitial lung disease	No. (%)	14 (4.8)	23 (4.5)
	IR	1.94	1.69
	95% CI	(1.17 to 3.22)	(1.13 to 2.52)
Malignant tumours	No. (%)	17 (5.9)	23 (4.5)
	IR	2.33	1.76
	95% CI	(1.47 to 3.69)	(1.19 to 2.61)
Major adverse cardiovascular event	No. (%)	3 (1.0)	4 (0.8)
	IR	0.39	0.28
	95% CI	(0.13 to 1.20)	(0.11 to 0.75)
Venous thromboembolism	No. (%)	–	–
	IR	–	–
	95% CI	–	–
Psoriasis	No. (%)	5 (1.7)	10 (1.9)
	IR	0.78	0.78
	95% CI	(0.35 to 1.73)	(0.43 to 1.40)
Systemic lupus erythematosus or lupus-like syndrome	No. (%)	1 (0.3)	4 (0.8)
	IR	0.13	0.28
	95% CI	(0.02 to 0.92)	(0.11 to 0.75)
Serious allergic reaction	No. (%)	–	–
	IR	–	–
	95% CI	–	–
Serious blood disorders	No. (%)	1 (0.3)	2 (0.4)
	IR	0.13	0.14
	95% CI	(0.02 to 0.92)	(0.04 to 0.56)
Demyelination	No. (%)	–	–
	IR	–	–
	95% CI	–	–
Hepatitis B DNA assay positive	No. (%)	5 (1.7)	5 (1.0)
	IR	0.65	0.35
	95% CI	(0.27 to 1.55)	(0.15 to 0.85)
Injection site reaction	No. (%)	7 (2.4)	13 (2.5)
	IR	9.70	5.99
	95% CI	(7.73 to 12.16)	(4.84 to 7.41)
Abnormal liver function tests	No. (%)	68 (23.4)	117 (22.8)
	IR	16.94	15.64
	95% CI	(14.27 to 20.10)	(13.71 to 17.84)

Each event consists of the number of subjects (%), number of events per 100 PY and 95% CI. A blank in the table indicates no event in the analysis.
IR, incidence rate; PY, person-year.

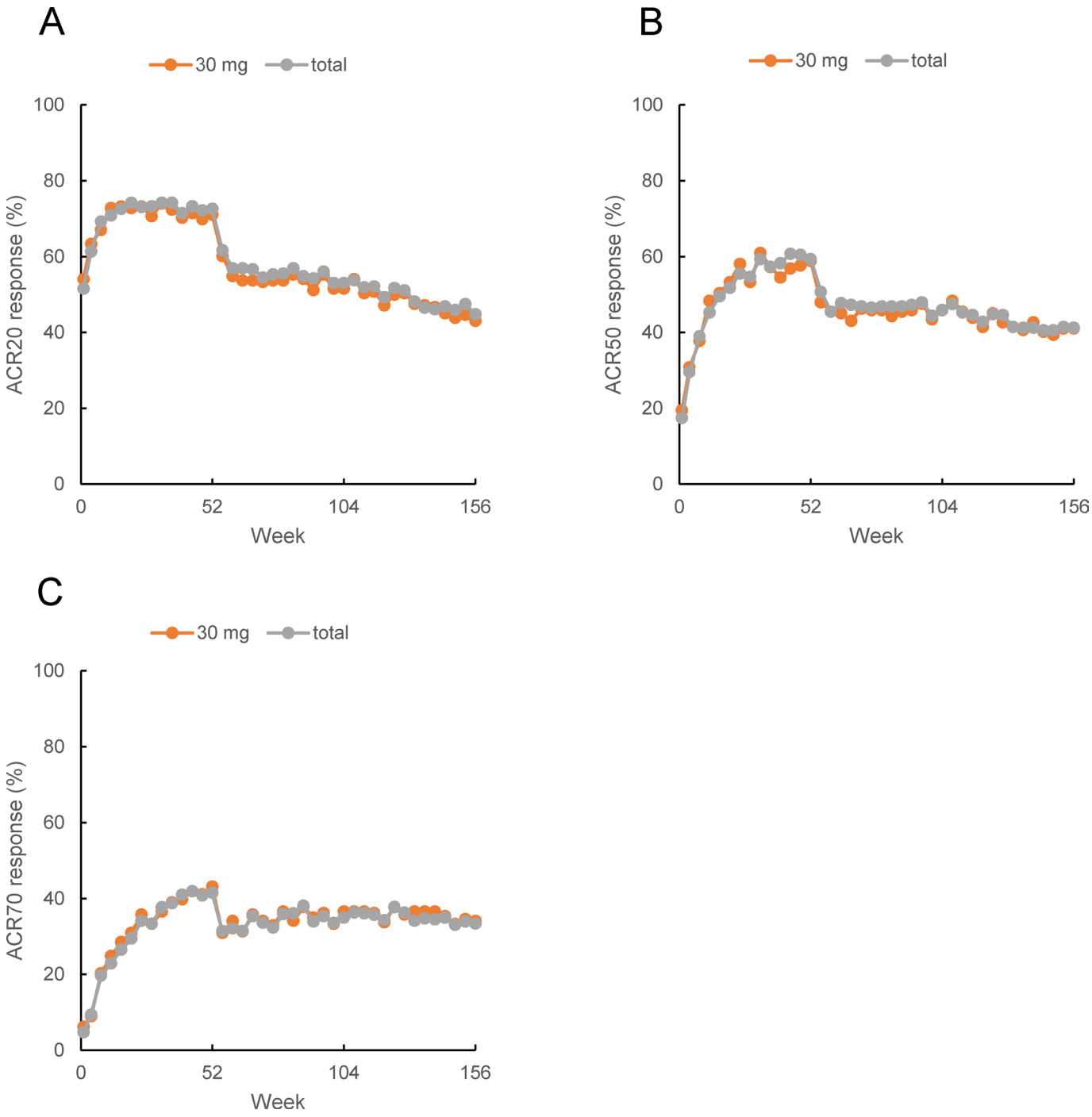

Figure 2 ACR20/50/70 responses through 156 weeks. (A) ACR20, (B) ACR50 and (C) ACR70 response in the 30 mg and total groups throughout the trials analysed by non-responder imputation. ACR, American College of Rheumatology.

stage of RA treatment.[32] Some malignant tumour cases may have been undetected by regular screening in these trials. Interstitial lung diseases also occurred at a higher level in the early period, which was consistent with global analysis of case reports.[33] Therefore, careful monitoring of these events would be required, especially at the early treatment stage. Additionally, tuberculosis was observed in a patient (0.2%) in this integrated analysis, which resulted in death. As with other TNFis, the risk of tuberculosis infection exists with this drug and all measures for early detection and treatment should be implemented when using this class of drugs.

Injection site reactions were observed in only 13 (2.5%) patients, which was less than other previously reported TNFis.[21 22] Furthermore, this analysis detected no serious allergic reaction. These unwanted immune responses were reported to be associated with immune response via Fcγ or complement receptor and size of immune complex.[34] The flexible molecular structure of ozoralizumab characterised by non-Fc region and non-formulation of huge

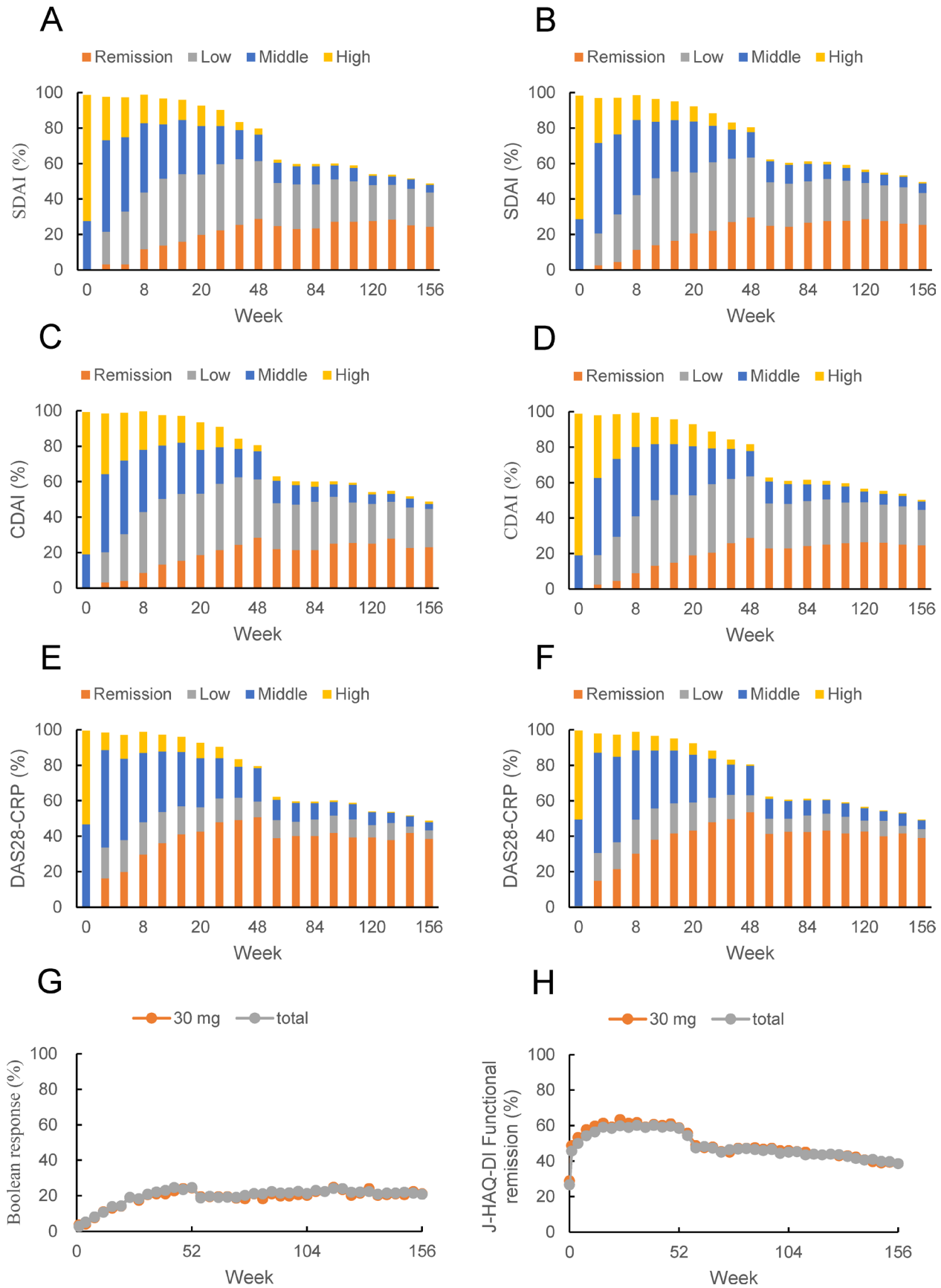

Figure 3 Categorical efficacy analysis through 156 weeks. (A) SDAI, (C) CDAI and (E) DAS28-CRP in the 30 mg group, (B) SDAI, (D) CDAI and (F) DAS28-CRP in the total group, and (G) Boolean remission and (H) HAQ-DI remission analysed by non-responder imputation. CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; J-HAQ-DI, Japanese Health Assessment Questionnaire Disability Index; SDAI, Simplified Disease Activity Index.

immune complexes may contribute to the reduction of local hypersensitivity reaction, and ozoralizumab-TNF immune complexes may not induce inflammation in an in vivo study.[10] Therefore, the unique structure of ozoralizumab was associated with these clinical benefits.

Immunogenicity for ozoralizumab was evaluated in the OHZORA and NATSUZORA trials but not in the HOSHIZORA trial because of patient burden. Discontinuation from the HOSHIZORA trial due to disease progression was reported in only 11 patients (5 from the OHZORA trial and 6 from the NATSUZORA trial), indicating less frequent disease flaring in the OHZORA trial with MTX, relative to the number of enrolled patients. However, the impact of secondary failure may have been limited even in the HOSHIZORA trial without MTX and the effect of immunogenicity on long-term use of ozoralizumab would require more investigations for a future challenge.

This integrated analysis shows the preferable efficacy of ozoralizumab in long-term use by NRI (figures 2 and 3). The OC analysis provided excellent results, similar to those of another TNFi analysed by OC in terms of long-term efficacy.[21 22] Some patients were not enrolled in the HOSHIZORA trial due to exclusion criteria, while others were excluded from efficacy analysis due to allowance windows. Based on these points, unnatural changes in efficacy rate after week 52 were observed (figures 2 and 3). Efficacy analysis revealed a better response in patients from the OHZORA trial than the NATSUZORA trial (online supplemental table 3), which indicated that MTX demonstrated an additional effect on ozoralizumab. Better efficacy in combination with bDMARDs and MTX was similarly reported as a meta-analysis.[35] However, the efficacy results in patients from the NATSUZORA trial also indicated a good response, and thus ozoralizumab could be a good potential option for patients intolerant of MTX.

The limitations of this integrated analysis should be considered as follows. Accidentally occurring safety events may have been overestimated because of the small total exposure, and thus additional investigation on a larger scale is warranted. The HOSHIZORA trial was an open-label trial without control group, thus this analysis was not designed to detect the statistical difference of safety and efficacy. The 80 mg dose of ozoralizumab was used until the approval submission dose of 30 mg was determined, which may have influenced safety and efficacy assessments. The evaluation of joint damage progression was not included in this analysis. All of the patients were Japanese and thus finding racial differences in response to ozoralizumab is impossible. Patients including discontinued ones were investigated only during ozoralizumab administration period.

In conclusion, this integrated analysis revealed that ozoralizumab was well tolerated, and its efficacy was maintained in the long-term administration.

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Contributors All authors met the following criteria for authorship: substantial contributions to the acquisition, analysis and interpretation of data for the work, contribution to drafting the work and revising it critically, giving the final approval of the version and agreeing to be accountable for all aspects of the work. TT takes responsibility for the overall contents as guarantor.

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Competing interests YT has received speaking fees and/or honoraria from AbbVie, Eisai, Chugai, Eli Lilly, Boehringer Ingelheim, GlaxoSmithKline, Taisho, AstraZeneca, Daiichi Sankyo, Gilead, Pfizer, UCB, Asahi Kasei, Astellas, received research grants from Boehringer Ingelheim, Taisho, Chugai. TT has received speaking fees and/or honoraria from AstraZeneca, Astellas Pharma, AbbVie, Chugai Pharmaceutical, Eisai, Eli Lilly Japan, Gilead Sciences, Mitsubishi-Tanabe Pharma, Taisho Pharmaceutical Holding, Pfizer Japan, Janssen Pharmaceutical, received consulting fees from AbbVie, Gilead Sciences, Mitsubishi-Tanabe Pharma, Taisho Pharmaceutical Holding, Eli Lilly Japan. YM, MK and HY are employees of Taisho Pharmaceutical.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The trials were approved by institutional review boards at every investigational site. Reference numbers or IDs were issued but not described here because of numerous sites for each three trials. All these trials were conducted in compliance with the ethical principles according to the Declaration of Helsinki, Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, and Ministerial Ordinance on Good Clinical Practice. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. Data generated and/or analysed in the current study were provided by Taisho Pharmaceutical and not publicly available. Requests for access to these data should be made to the corresponding author.

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