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COMB157G1401 Study Results Synopsis for Public Disclosure

Title	Special drug-use surveillance for Kesimpta s.c. injection 20 mg pen (relapsing-remitting multiple sclerosis and active secondary progressive multiple sclerosis, COMB157G1401)
NIS type	NIS with Primary Data Collection; Novartis Drug NIS
Keywords	Japan, ofatumumab (genetical recombination), relapsing-remitting multiple sclerosis and active secondary progressive multiple sclerosis, non-interventional study, post-marketing surveillance
Rationale and background	This special drug-use surveillance compliant with good post-marketing study practice (GPSP) was conducted primarily to evaluate the long-term safety and tolerability of Kesimpta in clinical use. The reasons for conducting the surveillance are as follows: only a limited number of Japanese patients was included in the clinical study of Kesimpta for patients with multiple sclerosis (MS); the patient profiles of the clinical study excluded patients who were supposed to receive Kesimpta in clinical use but considered at relatively high risk of infection; and the observation periods were scheduled for a limited period of time.
Research objectives	To evaluate the long-term safety etc. of Kesimpta in clinical use in patients with relapsing-remitting MS (RRMS) and patients with active secondary progressive multiple sclerosis (SPMS)
Study design	This study is an uncontrolled, central registration system, open-label, multicenter observational study in patients using Kesimpta for the labeled indication.
Population	Inclusion criteria 1. Patients must provide written consent to participate in this study before the start of treatment with Kesimpta 2. Patients using Kesimpta for the first time for the following indication Prevention of relapses and prevention of physical disability progression in the following patients • RRMS • Active SPMS Exclusion criteria 1. Patients with a history of treatment with a drug containing the same ingredient as Kesimpta (investigational drug or post-marketing clinical study drug) 2. Patients with a history of hypersensitivity to any of the Kesimpta ingredients

Variables	Patient characteristics, data on Kesimpta administration, Kesimpta discontinuation status, concomitant medications, medications used for the underlying disease after Kesimpta discontinuation, laboratory tests, presence/absence of pregnancy and nursing status (present/absent), Physician's Global Assessment of disease activity (PGA), Expanded Disability Status Scale (EDSS), number of gadolinium-enhancing lesions on magnetic resonance imaging (MRI), clinical relapses, adverse events
Results	[Study outline] • This study was started on May 19, 2021 and completed on May 13, 2025. The case report form (CRF) data of 367 patients were locked during the study period. The safety analysis set consisted of 365 patients after excluding 2 patients from the 367 patients for whom CRF data were locked. The reasons for exclusion were "physician's signature absent" in 2 patients and "off label use" in 1 patient (including duplicate patients). The effectiveness analysis set consisted of the 338 patients after excluding the 27 patients who did not have any PGA records or implementation from the safety analysis set. • The safety analysis set (365 patients) in this study consisted of 31.0% (113 patients) men and 69.0% (252 patients) women. The mean (standard deviation, hereafter called SD) age at the start of treatment with Kesimpta administration was 42.3 (11.21) years. For disease types, RRMS accounted for 79.7% (291 patients) and active SPMS accounted for 20.3% (74 patients). The proportion of patients free from MS relapse during the 12 months before the start of treatment with Kesimpta was 48.2% (176 patients). The proportion of patients by category of EDSS score at the start of treatment with Kesimpta administration was 0 to 1.5 in 26.8% (98 patients), 2.0 to 3.0 in 20.3% (74 patients), 3.5 to 6.0 in 24.7% (90 patients), and 6.5 to 9.5 in 10.1% (37 patients). • For the 365 patients in the safety analysis set of this study, the median (minimum – maximum) duration of treatment with Kesimpta (including the dose-free period) was 710.0 (1–820) days, and the total duration of exposure was 640.2 patient-years. The duration of treatment with Kesimpta (including the dose-free period) was 24 weeks or longer in 94.2%, 48 weeks or longer in 88.2%, and 72 weeks or longer in 84.9%. All the doses of Kesimpta were administered at 20 mg/dose. [Safety] • The incidence of adverse reactions (were defined as adverse events for which a causal relationship with Kesimpta could not be ruled out by the investigator) was 21.1% (77/365 patients). Adverse reactions reported in ≥ 3.0% of patients by PT were pyrexia in 7.4% (27/365 patients), headache in 3.8% (14/365 patients), and COVID-19 in 3.3% (12/365 patients). • The number of patients with adverse reactions by timing of initial onset was 35 patients from the start of treatment to Day 7 (365 patients), 7 patients from Days 8 to 30 (365 patients), 14 patients from Days 31 to 180 (361 patients), 11 patients from Days 181 to 360 (350 patients), 6 patients from Days 361 to 540 (333 patients), 3 patients from Days 541 to 720 (316 patients), and 1 patient from Day 721 onward (199 patients). There was no tendency for the incidence of adverse reactions to increase with long-term treatment.

	• The incidence of serious adverse reactions was 3.3% (12/365 patients). Serious adverse reactions reported in ≥ 2 patients by PT were COVID-19 and multiple sclerosis relapse, and the incidence was 0.5% (2/365 patients) for both of these events. The outcome of these adverse reactions was resolved and resolving in 1 event each. • The incidence of adverse events that led to the discontinuation of Kesimpta was 4.1% (15/365 patients). Adverse event that led to treatment discontinuation reported in ≥ 2 patients by PT was only multiple sclerosis (3/365 patients, 0.8%). In addition, only 1 patient discontinued treatment due to multiple sclerosis relapse. • There was 1 death due to an adverse event, acute myeloid leukaemia (term entered by physician: worsening of acute myeloid leukemia). This patient had acute myeloid leukaemia as a complication, and the event was considered unrelated to Kesimpta by the investigator. • The incidence of adverse events corresponding to safety specifications was 11.5% (42/365 patients) for “infections” and 12.6% (46/365 patients) for “injection-related systemic reactions.” • Of “infections,” the incidence of herpes zoster as an adverse reaction was 0.3% (1/365 patients). Of adverse reactions in the SOC “infections and infestations,” the most common adverse reaction of COVID-19 (12 patients) was variable in timing of initial onset, with no consistent trend observed. • At the time of the first dose, the incidence of “injection-related systemic reactions” (adverse events) was 8.6% (12/139 patients) in the patients without the use of premedication, and 5.6% (3/54 patients), 4.4% (5/113 patients) and 20.3% (12/59 patients) in the patients with the use of premedications (steroid only, steroid and non-steroid, and non-steroid only), respectively. The incidence of “injection-related systemic reactions” was higher in the patients who used only non-steroid as premedication than in the patients without the use of premedication. • During the Kesimpta treatment period, the median values of white blood cell counts, lymphocytes (%), neutrophils (%), and IgG remained unchanged up to 24 months after the start of treatment. The median values of IgM showed a decreasing trend from the start of treatment to 24 months. B-cell counts mostly depleted following treatment with Kesimpta administration. • When the incidences of adverse reactions were compared in the patient factors, the only factor for which the 95% CI of the odds ratio within the category did not include 1 was the presence or absence of complication (hepatic impairment). The incidence of adverse reactions by presence or absence of hepatic impairment was higher in the patients with hepatic impairment (40.0%, 10/25 patients) than in the patients without hepatic impairment (19.7%, 67/340 patients), however the outcome of all the adverse reactions in the patients with hepatic impairment was resolved or resolving except for 1 event. • The incidence of adverse reactions in the elderly patients aged ≥ 65 years (9.1%, 1/11 patients) was lower than that in the non-elderly patients (21.5%, 76/354 patients). In addition, 2 children aged < 18 years were registered, however no adverse events were observed. Patients with renal impairment as a complication were not registered. • Four pregnancies were reported during the observation period of this study. One of these patients continued treatment with Kesimpta during

	pregnancy, and the pregnancy resulted in abortion. Both pregnancy and abortion in this patient were reported as adverse events. The investigator assessed the abortion as being related to Kesimpta; however, other factors than Kesimpta included concurrent COVID-19 around the onset of abortion. No adverse events were reported during the period of this study for pregnancies in the 3 remaining patients. Detailed information on the status of the fetus was unknown. • The incidence or severity of infection did not tend to increase even when a white blood cell count, neutrophil count, IgG, or IgM decreased during treatment with Kesimpta. [Effectiveness] • PGA of the 338 patients in the effectiveness analysis set by evaluation time point at 12 months from the start of Kesimpta treatment (272 patients) was 3.7% for very much improved, 27.6% for improved, 63.6% for unchanged, and 5.1% for worsening. No patients had PGA not assessable. At 24 months from the start of Kesimpta treatment (223 patients), PGA was very much improved in 2.7%, improved in 15.7%, unchanged in 75.3%, and worsening in 6.3%. No patients had PGA not assessable. At final evaluation (338 patients), PGA was very much improved in 2.4%, improved in 14.5%, unchanged in 75.4%, and worsening in 7.1%. PGA was not assessable in 0.6% of the patients. • The annualized relapse rate after treatment with Kesimpta administration (95% CI) was 0.09 (0.07−0.12) times/year in the overall effectiveness analysis set. • The mean (SD) EDSS at the start of treatment with Kesimpta administration in the effectiveness analysis set was 3.01 (2.264). The mean (SD) change in EDSS at 3 months, 6 months, 12 months, 24 months from the start of treatment with Kesimpta and at final evaluation was -0.13 (0.513), -0.12 (0.528), -0.14 (0.620), -0.14 (0.690), and -0.11 (0.682), respectively, showing very small changes. No apparent change in the mean EDSS score was observed during the Kesimpta treatment period. • For the 338 patients in the effectiveness analysis set, the point estimate (95% CI) of the proportion of patients showing confirmed disability worsening on EDSS sustained over ≥ 3 months based on the Kaplan-Meier method was 2.0% (0.8−4.7), 3.3% (1.7−6.5), and 3.3% (1.7−6.5) at 12 months, 24 months from the start of treatment with Kesimpta and at final evaluation, respectively. The point estimate (95% CI) for the proportion of patients with confirmed disability worsening on EDSS sustained over ≥ 6 months was the same as proportion of patients with confirmed disability worsening on EDSS sustained over ≥ 3 months and remained at a low level. • For the 338 patients in the effectiveness analysis set, the point estimate (95% CI) of the proportion of patients showing confirmed disability improvement on EDSS sustained over ≥ 6 months based on the Kaplan-Meier method was 7.1% (4.6−10.9), 8.0% (5.3−12.0), and 8.0% (5.3−12.0) at 12 months, 24 months from the start of treatment with Kesimpta and at final evaluation, respectively. • For the response rate (very much improved + improved) on PGA, the 95% CI of the adjusted odds ratio by patient factor did not include 1 for “age category (median): ≥ 43.0 years,” “weight category: > 40 kg,” and “presence/absence of MS relapse in the 12 months before the start of

	Kesimpta treatment: 0 times." The response rate (very much improved + improved) was higher in the patients aged < 43.0 years than in the patients aged ≥ 43.0 years, the patients with body weight ≤ 40 kg than in the patients with body weight > 40 kg, and the patients with MS relapse ≥ once in the 12 months before the start of Kesimpta treatment than patients with MS relapse 0 times, respectively. • For the response rate including "unchanged" (very much improved + improved + unchanged) on PGA, the 95% CI of the adjusted odds ratio by patient factor did not include 1 for only "age category (median): ≥ 43.0 years." The response rate (very much improved + improved + unchanged) was higher in the patients aged < 43.0 years than in the patients aged ≥ 43.0 years. • For the incidence of clinical relapse, the 95% CI of the adjusted odds ratio by patient factor did not include 1 for "presence/absence of MS relapse in the 12 months before the start of Kesimpta treatment: 0 times" and "total EDSS at baseline: 3.5−6.0".Patients who had experienced at least 1 MS relapse in the last 12 months prior to starting treatment had more relapses than those who had no relapses (18.0% [23/128 patients] vs. 5.7% [8/141 patients]). Clinical relapse was more frequent in patients with baseline total EDSS of 3.5-6.0 than in those with baseline total EDSS of 0-1.5 (21.1% [16/76 patients] vs. 6.5% [6/92 patients])." • PGA at final evaluation in patients with special characteristics was very much improved and unchanged in 1 patient each among the children aged < 18 years (2 patients). In the elderly aged ≥ 65 years (10 patients), PGA was unchanged in 9 patients and worsening in 1 patient. PGA was unchanged in the pregnant women (3 patients). In this study, 24 patients with a complication of hepatic impairment (7.1%) were registered, and the response rate including "unchanged" (very much improved + improved + unchanged) on PGA was 91.7% (22 patients), which was comparable to the response rate of 92.4% (290/314 patients) in the patients without such a complication.
Conclusion	In this study, patients with RRMS and patients with active SPMS received long-term treatment with Kesimpta for up to 24 months under the actual use conditions in Japan. The safety and effectiveness of Kesimpta obtained in this study did not tend to be significantly different from the clinical study data used for the approval application, and Kesimpta was suggested to be useful under the conditions of actual use in Japan as long as the safety management rules specified in the existing package insert are complied with.

1 List of abbreviations

Abbreviations	Full forms (English)
CI	confidence interval
COVID-19	coronavirus disease 2019
EDSS	Expanded Disability Status Scale
GPSP	good post-marketing study practice
IgG	immunoglobulin G
IgM	immunoglobulin M
MRI	magnetic resonance imaging
MS	multiple sclerosis
NIS	non-interventional study
PGA	physician's global assessment
PT	preferred term
RRMS	relapsing-remitting multiple sclerosis
SOC	system organ class
SPMS	secondary progressive multiple sclerosis