Date: 24 October 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Zeposia

International non-proprietary name: ozanimod as ozanimod hydrochloride

Pharmaceutical form: hard capsules

Dosage strength(s): 0.23 mg, 0.46 mg, and 0.92 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Bristol-Myers Squibb SA

Marketing Authorisation No.: 67046

Decision and Decision date: extension of therapeutic indication approved on 19 August 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{ss}	Area under the plasma concentration-time curve in steady state
CI	Confidence interval
$C_{max,ss}$	Maximum observed plasma/serum concentration of drug in steady state
CYP	Cytochrome P450
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
IBD	Inflammatory bowel disease
IP	Induction period
IR	Incidence rate
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAO-B	Monoamine oxidase B
MP	Maintenance period
MS	Multiple sclerosis
OLE	Open-label extension
OLP	Open-label period
OZA	Ozanimod
PBO	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PopPK	Population pharmacokinetic
PRES	Posterior reversible encephalopathy syndrome
RMP	Risk Management Plan
RMS	Relapsing multiple sclerosis
S1P	Sphingosine 1-phosphate
S1P1	Sphingosine 1-phosphate receptor type 1
S1P5	Sphingosine 1-phosphate receptor type 5
SwissPAR	Swiss Public Assessment Report
SY	Subject year
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Ulcerative colitis
ULN	Upper limit of normal

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, are no longer responding, or are intolerant to conventional therapy or treatment with a biologic agent.

2.2.2 Approved Indication

Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended target dose is 0.92 mg, orally once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	21 December 2020
Formal control completed	19 January 2021
List of Questions (LoQ)	31 August 2021
Answers to LoQ	29 October 2021
Predecision	11 January 2022
Answers to Predecision	10 March 2022
Labelling corrections	5 May 2022
Answers to Labelling corrections	2 June 2022
Labelling corrections 2nd round	22 July 2022
Answers to Labelling corrections 2nd round	3 August 2022
Final Decision	19 August 2022
Decision	approval

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3 Medical Context

Ulcerative colitis (UC) is a life-long inflammatory bowel disease (IBD) of multifactorial aetiology with an abnormal mucosal immune response against commensal non-pathogenic bacteria of the colon, resulting in bowel inflammation. The age of onset varies from 15 to 40 years. Its prevalence has constantly increased, reaching a plateau in recent years. UC is characterised by recurrent episodes of mucosal inflammation of the colon, mainly involving the rectum and potentially progressing to the proximal colon. Symptoms related to the intestinal inflammation include diarrhoea with and without blood, increased frequency and reduced volumes of bowel movements, abdominal pain, urgency and stool incontinence. Clinical management and long-term outcome depend on disease severity, as assessed by clinical disease activity indices such as the Mayo Score. Long-term complications include stricture, dysplasia and colorectal cancer. With respect to the latter, the risk increases with the duration and extent of UC. Mortality overall is slightly increased, but recent improvements in disease management have led to a decline in mortality rates. The long-term treatment goal for active UC is to achieve glucocorticoid-free remission. While induction therapies induce a relatively rapid onset of action, maintenance therapies have been shown to be effective in the long-term therapeutic setting. Glucocorticoid-sparing treatment options such as immunomodulators (e.g. 6-mercaptopurine, azathioprine or methotrexate) have a specific risk profile (e.g. malignancy, bone marrow suppression), require regular laboratory monitoring and share a delayed onset of action (up to 12 weeks for full remission). Some drugs such as biologic agents have been found to be effective in both the induction and maintenance period. Biologic agents including monoclonal antibodies (mAbs) directed against the cytokine tumour necrosis factor (TNF) (i.e. infliximab, adalimumab and golimumab), the janus kinase inhibitor tofacitinib, the monoclonal anti-integrin α4β7 antibody vedolizumab and the monoclonal anti-interleukin-12/23 antibody ustekinumab have been authorised in Switzerland for moderate to severe UC.

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4 Nonclinical Aspects

In vitro data showed that ozanimod and its seven metabolites actively bind to human sphingosine 1-phosphate receptor type 1 (S1P1) and type 5 (S1P5). The data suggested that the metabolites of ozanimod are able to compete for the same binding site as the parent molecule. Ozanimod and its metabolites exhibited activity profiles on cynomolgus monkey S1P1 and S1P5 that are similar to the activities on human S1P1 and S1P5.
In a rat model of Inflammatory Bowel Disease (IBD), ozanimod hydrochloride improved the colonic pathology. The compound also exerted a beneficial effect on CD4+ adaptive transfer-induced IBD as determined by evaluation of clinical and histopathologic parameters in a mice model of IBD. There are no changes with regard to posology and method of administration.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

The pharmacokinetics of ozanimod and its active main metabolite CC112273 in UC patients was investigated in two separate population pharmacokinetic (popPK) analyses. The main objective of these analyses was to evaluate potential pharmacokinetic differences between healthy subjects, relapsing multiple sclerosis (RMS) patients and UC patients. As the pharmacological activity of CC112273 is similar to that of ozanimod, and its plasma concentrations are considerably higher, the metabolite is the main driver of efficacy.

The datasets included six Phase 1 studies in healthy subjects, one Phase 1 study in RMS patients, one Phase 2 study in UC Patients, two Phase 3 studies in RMS patients and one Phase 3 study in UC patients.

The overall approach of model development was the same for ozanimod and CC112273. The base model of the current analyses was the final model of previous popPK analyses. Additional potential covariate relationships were investigated by univariate screening and a full model approach. The final model was determined by backward elimination of covariate relationships from the full model. Only the newly added covariate relationships were subjected to the backward elimination. The previous covariate relationships remained in the model, even if they were not statistically significant.

CC112273
The CC112273 dataset included 2890 individuals, of whom 259 (9%) were healthy subjects, 1746 (60.4%) were RMS patients and 885 (30.6%) were UC patients. There were no subjects with severe renal or hepatic impairment in the dataset, but there was an adequate number of subjects with mild or moderate renal or hepatic impairment. The inclusion of the UC patients resulted in an extension of the age range from 18 to 55 years to 18 to 74 years.
Of the covariate relationships included in the final model, the largest effects were observed for smoking status on apparent clearance (CL/F), sex on CL/F, apparent volume of the central compartment (VC/F) and absorption constant (KA) and body weight on VC/F and KA. However, the overall effect of the covariates on CC112273 exposure ($C_{max,ss}$ and AUC_{ss}) was small:

- The mean CC112273 tt,ss and AUC_{ss} in smokers were about 56 % lower than in non-smokers in the overall population included in the popPK analysis. In UC patients, the difference in CC112273 exposure between smokers and non-smokers was about 44%. The effect of smoking on CC112273 exposure is known from previous popPK analyses and is considered to be due to differences in MAO-B expression between smokers and non-smokers (CC112273 is formed by MAO-B).

- The mean CC112273 exposure was 32% higher in women compared to men in the overall population. In UC patients, the difference was about 36 %.

- The CC112273 exposure was similar in patients ≤ 60 kg and > 80 kg in the overall population and in UC patients.

- The CC112273 exposure in healthy subjects, RMS patients and UC patients was similar.

- The mean CC112273 exposure was 42% higher in subjects >65 years compared to subjects ≤45 years in the overall population. In UC patients, who “contributed” the older patients, the difference was only 27%. The dataset included 37 (UC) patients > 65 years. From a pharmacokinetic point of view, this is sufficient to conclude that CC112273 PK is not affected by age. However, it needs to be considered that no clinical efficacy and safety data were available for RMS patients >55 years

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of age.

- In the overall population, the CC112273 exposure was similar in subjects with normal renal function and mild renal impairment. In subjects with moderate renal impairment, $C_{max,ss}$ and AUC_{ss} were 47% and 48% higher, respectively, compared to subjects with normal renal function. In UC patients, the corresponding differences were 20% ($C_{max,ss}$) and 14 % (AUC_{ss}).

- The estimated CC112273 AUC was 56% higher in the presence of gemfibrozil. In UC patients, it was 46% higher in the presence of CYP2C8 inhibitors. These results were in good agreement with the results of the respective interaction study (CC112273 AUC 47% ↑).

- The co-administration of prednisolone had no effect on CC112273 exposure in the overall population or in UC patients.

The final model described the CC112273 data sufficiently well to be suitable for simulations.

Ozanimod
The ozanimod dataset included 2977 individuals, of whom 257 (8.6%) were healthy subjects, 1748 (58.7%) were RMS patients and 972 (32.7%) were UC patients. There were no subjects with severe renal or hepatic impairment in the dataset, but there was an adequate number of subjects with mild or moderate renal or hepatic impairment. As for the metabolite, the inclusion of the UC patients resulted in an extension of the age range from 18 to 55 years to 18 to 74 years.

Of the covariate relationships included in the final model, age and body weight had the largest effects on ozanimod exposures. As for the metabolite, the effect of the covariates on ozanimod exposure was small.

- The ozanimod exposure was similar in healthy subjects, RMS patients and UC patients.

- The mean ozanimod $C_{max,ss}$ and AUC_{ss} in subjects ≤ 60 kg were 36% and 30% higher, respectively, compared to subjects > 80 kg.

- The mean ozanimod $C_{max,ss}$ and AUC_{ss} in subjects > 65 years were 16% and 18% higher, respectively, compared to subjects ≤ 45 years.

The final model described the ozanimod data sufficiently well to be suitable for simulations.

In summary, the results of the popPK analyses were in agreement with the results of the previous analyses including healthy subjects and RMS patients only. There were no clinically relevant pharmacokinetic differences between healthy subjects, RMS patients and UC patients.

Exposure-Response Relationships
Efficacy
The exposure-response analyses for efficacy indicated a difference between placebo and ozanimod treatment, but no clear relationship to CC112273 AUC. As only one dose level was investigated and CC112273 has a long half-life, this was to be expected. While the probability of clinical remission was higher for less severely ill patients, a difference between placebo and ozanimod treatment was visible for the more severely ill patients as well.

Safety
The probability of experiencing increased AST/ALT values or infections increased with increasing CC112273 exposure, even if it was not a statistically significant predictor. The probability of experiencing high AST/ALT values, but not the risk for infections, was higher in UC patients than in RMS patients.

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5.2 Dose Finding and Dose Recommendation

Dose Finding

Phase 2 study RPC01-202 had demonstrated that 1 mg ozanimod (OZA) was effective for the induction and maintenance of the pre-specified efficacy endpoints *clinical remission, clinical response, endoscopic improvement*, and *histologic remission* (for definitions see *5.3 Efficacy)*. The comparison of the effects on clinical endpoints for the OZA 0.5 mg and 1.0 mg doses and the placebo (PBO) groups suggested a dose-response relationship. An additional long-term dose-response analysis of clinical response outcomes at the end of the treat-through maintenance period (MP) (33 weeks) of study RPC01-202 further corroborated the assumption of a dose-response relationship. The dose-response analysis identified a target dose of 0.96 mg (95% CI: 0.70, 1.42 mg) as the optimal dose. There was no dose effect for overall treatment-emergent adverse events (TEAEs), or for severe, serious, or suspected related TEAEs. The favourable benefit-risk in Phase 2 study RPC01-202 provided support for the optimal dose being 1 mg. The clinical data from Study RPC01-3101 then confirmed OZA 1 mg as the recommended dose for the treatment of adult patients with moderate to severe UC. The safety profile was consistent with the Phase 2 RPC01-202 study and with the multiple sclerosis clinical programme, with no new emerging safety signals. The recommended dose for the treatment of multiple sclerosis is also 0.92 mg OZA once daily orally.

Dose Recommendation

In UC, the recommended dose is 0.92 mg ozanimod once daily. During the initiation of OZA treatment, the risk for bradyarrhythmia is known to be increased due to the effect on the S1P1 receptor. Therefore, an initial dose escalation regimen of ozanimod is required, with 0.23 mg OZA from days 1 to 4, and 0.46 mg OZA from days 5 to 7 once daily. The maintenance dose of 0.92 mg once daily starts on day 8. Prior to treatment initiation, an ECG recording is recommended for all patients. Additional cardiac monitoring over 6 hours is recommended in patients with pre-existing risk factors (see Information for Healthcare Professionals).

5.3 Efficacy

The development programme for the use of OZA in UC comprises three studies: RPC01-202, RPC01-3101, and RPC01-3102 OLE (Open-Label Extension). Evaluation of efficacy in the proposed indication is based on pivotal Phase 3 study RPC01-3101 and the supportive Phase 2 study RPC01-202. Both were designed to evaluate the treatment effect of OZA in moderate to severe UC using different but complementary study designs (treat-through versus randomised withdrawal) with an Induction Period (IP) and a Maintenance Period (MP), with the objective of demonstrating efficacy at the end of each period.

The pivotal Phase 3 Study RPC01-3101 is a completed Phase 3, multicentre, randomised, double-blind, treat-through, PBO-controlled parallel-group study to evaluate the clinical efficacy and safety of oral OZA 1 mg/d vs. PBO in adult patients with moderate to severe active UC, including a PBO-controlled IP and a randomised withdrawal MP with separate randomisations and, consequently, separate analyses. The IP had two cohorts: Cohort 1 was a PBO-controlled cohort serving for the primary analyses of induction, while Cohort 2 was an open-label arm that aimed to provide an adequate sample size for the following MP. In the MP, Cohort 1 subjects receiving OZA and all Cohort 2 subjects who completed the IP and had a clinical response at week 10 (based on either 3- or 4-component Mayo score) could continue in the MP. They were re-randomised to either OZA or PBO. Cohort 1 participants previously randomised to PBO in the IP with a clinical response at Week 10 could continue in the MP to receive PBO, or could continue in RPC01-3102 OLE. RPC01-3102 OLE study included Cohort 1 and 2 subjects without a clinical response at week 10, subjects with a relapse during the MP and subjects who completed the MP.
Moderately to severely active UC was defined as a 4-component Mayo score of 6 to 12 inclusive, with an endoscopic subscore of ≥ 2, rectal bleeding score of ≥ 1, and stool frequency score ≥ 1. Inclusion required current treatment with at least one of the following therapies, which had to be continued in the IP: oral aminosalicylates/prednisone/budesonide multi matrix. Patients with an abnormal ECG, history of uveitis or macular oedema, severe pulmonary disease, Forced Expiratory Volume in 1

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second (FEV1) or Forced Vital Capacity (FVC) < 70% of predicted values at Screening, and primary non-responders to two or more biologic agents for UC were excluded from participation (list of exclusion criteria incomplete).

Permitted concomitant treatment
5-Aminosalicylic acid (5-ASA) at a stable dose was allowed during the IP and MP. Corticosteroids at a stable dose during the IP. During the MP, tapering was required upon entering the MP at IP week 10 with tapering intervals depending on the daily dose taken.

Patient characteristics
Induction Period (IP)
Overall, 1012 subjects were enrolled in the IP, with 645 in Cohort 1 (mean age 41.5 years (range 18 – 74), mean disease duration 7.81 years (range 0-49.1), median baseline 4-component Mayo Score 9.0 (range 6-12)). In Cohort 1, 216 subjects were randomised to PBO and 467 to OZA 1 mg. Demographics, baseline disease characteristics and history of prior UC and concomitant medications (conventional as well as biologics) of subjects randomised in the IP were sufficiently balanced between groups. 367 subjects were included in open-label Cohort 2. At the end of the IP, 31.9% of Cohort 1 PBO treated, 54.3% of Cohort 1 and 61% of Cohort 2 OZA treated subjects achieved *clinical response* at Week 10 and could be re-randomised.
Maintenance Period (MP)
Overall, 526 subjects were enrolled in the MP (mean age of re-randomised subjects 42.7 years (range 18 - 74), mean disease duration 8.73 years (range 0 - 49.1 years), median baseline 4-component Mayo Score at baseline 9 (range 6 - 12). 227 subjects with clinical response at IP week 10 were re-randomised to PBO (117 from cohort 1), 230 to OZA 1mg (116 from Cohort 1). 69 subjects continued on PBO from the IP (all from Cohort 1). Demographics, disease characteristics and history of prior UC medications (conventional as well as biologics) among subjects who were re-randomised in the MP were consistent with those observed for Cohort 1 randomisation groups and sufficiently balanced between groups.

Efficacy measures
Standard IBD efficacy variables were applied to assess efficacy of OZA in UC in phase 2 study RPC01-202 and phase 3 study RPC01-3101 according to the CHMP guidance document for medicinal products to treat patients with UC (CHMP/EWP/18463/2006 dated 2008).
Scoring for the 4-component Mayo-Score (range 0 to 12):

Stool frequency[a]	Rectal bleeding[b]	Findings on endoscopy	Physician's Global Assessment[c]
0 = Normal number of stools for this subject, prior to the onset of UC disease, or while in remission 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal	0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, does not include friability) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)	0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease

UC = ulcerative colitis.
[a] Each subject served as his or her own control to establish the degree of abnormality of the stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] The Physician's Global Assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject's performance status.

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Term	Definition
Mayo Score	
3-component Mayo score	The sum of the RBS, SFS, and the endoscopy subscore. Each subscore has a range of 0 to 3 points and the 3-component Mayo score has a range of 0 to 9 points.
4-component Mayo score	The sum of the RBS, SFS, endoscopy, and PGA subscore. The 4-component Mayo score has a range of 0 to 12 points.
Partial Mayo score	The sum of the RBS, SFS, and PGA. The partial Mayo score has a range of 0 to 9 points
Clinical Remission (Primary Endpoint)	
3-component Mayo definition (RPC01-3101)	RBS = 0 and SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS) and endoscopy subscore ≤ 1 without friability
4-component Mayo definition (RPC01-202)	A 4-component Mayo score of ≤ 2 points with no individual subscore of > 1 point
Clinical Response	
3-component Mayo definition	A reduction from baseline in the 3-component Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point
4-component Mayo definition	A reduction from baseline in the 4-component Mayo score of ≥ 3 points and ≥ 30%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point
Endoscopic Improvement	Endoscopy subscore ≤ 1 (RPC01-202) Endoscopy subscore ≤ 1 without friability (RPC01-3101)
Histologic Remission	Geboes score < 2.0 (no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils in the lamina propria, and no crypt destruction, erosions, ulcerations, or granulation tissue)
Mucosal Healing	Endoscopic improvement with histologic remission (endoscopy subscore ≤ 1 without friability and a Geboes score < 2.0)
Corticosteroid-free Remission	Clinical remission while off corticosteroids for ≥ 12 weeks (Studies RPC01-3101 and RPC01-3102 only)
Maintenance of Remission	Clinical remission at Week 52 in the subset of subjects who are in remission at Week 10 (Study RPC01-3101 only)
Durable Clinical Remission	Clinical remission at Week 10 and at Week 52 in all subjects who entered the Maintenance Period (Study RPC01-3101 only)

5-ASA = 5-aminosalicylic acid; PGA = physician global assessment; RBS = rectal bleeding subscore; SFS = stool frequency subscore; TNF = tumor necrosis factor; UC = ulcerative colitis.

Analysis populations

The intention-to-treat (ITT) population was used as the primary population for all efficacy parameters**.** Cohort 1 included all randomised patients from Cohort 1 of the IP of the trial who received at least one dose of investigational drug (RPC1063 or PBO). Cohort 2 included all enrolled patients from Cohort 2 of the IP of the trial who received at least one dose of investigational drug.
The per-protocol (PP) population was used for the sensitivity analysis of clinical remission and additional analysis of clinical response to evaluate the influence of major protocol violators and protocol deviators on the primary results.

Statistical analysis

Analyses of efficacy and pharmacodynamics (PD) biomarker data were conducted in the ITT cohort by treatment/cohort. Primary and key secondary endpoints in the IP and MP were subject to a closed, hierarchical testing procedure for the primary and key secondary endpoints in order to control the overall type I error rate (family-wise error rate) for testing of these multiple endpoints. Multiplicity of testing in the MP did not address multiplicity arising from the IP as these were considered as two separate parts of the study. IP Cohort 1 was used to formally assess the efficacy endpoints in the IP. Cohort 2 IP was open-label, and no formal analysis of efficacy endpoints was conducted. Primary analysis of the primary endpoint of the proportion of patients in the composite score clinical remission at the end of the study period (either Week 10 or Week 52) was carried out using the Cochran-Mantel-Haenszel test at the two-sided 5% level of significance, stratified by anti-TNF use (yes/no) (IP), clinical remission status at Week 10 (MP) (yes/no), and corticosteroid use at screening

(IP)/Week 10 (MP) (yes/no)). For subjects meeting the treatment failure criteria prior to the end of the respective study period visit, their clinical remission was imputed using non-responder imputation. All key secondary efficacy endpoints were tested using the same type of Cochran-Mantel-Haenszel test as specified for the primary endpoint.

Efficacy endpoints

Endpoint	**IP: Cohort 1 (OZA vs. PBO)**
Primary	-Proportion of adult patients in *clinical remission* at Week 10
Key secondary	-Proportion of adult patients with a *clinical response* at Week 10 -Proportion of adult patients with *endoscopic improvement* at Week 10 -Proportion of adult patients with *mucosal healing* at Week 10
Endpoint	**MP (OZA-OZA vs. OZA-PBO)**
Primary	-Proportion of adult patients in *clinical remission* at Week 52
Key secondary	-Proportion of adult patients with a *clinical response* at Week 52 -Proportion of adult patients with *endoscopic improvement* at Week 52 -Proportion of adult patients in clinical remission at 52 weeks in the subset of patients who were in remission at Week 10 (*maintenance of remission*) -Proportion of adult patients with *corticosteroid-free remission* -Proportion of adult patients with *mucosal healing* at 52 weeks -Proportion of adult patients with *durable clinical remission*

IP Cohort 1 efficacy results

IP primary endpoint clinical remission

Despite a relatively short treatment duration of 9 weeks, a significantly larger proportion of subjects treated with OZA (18.4%) achieved clinical remission vs. the PBO group (6.0%) (Treatment difference 12.4%, 95% CI 7.5, 17.2; odds ratio 3.586, 95% CI 1.938, 6.636, p<0.0001). *Sensitivity analyses* yielded similarly highly significant results.

IP key secondary endpoints

Results for clinical response, endoscopic improvement, mucosal healing were consistent with the findings for the primary endpoint. In brief, 47.8% of OZA treated vs. 25.9% of PBO treated subjects achieved clinical response (p<0.0001). Endoscopic improvement was achieved in 27.3% of OZA treated vs. 11.6% of PBO treated subjects (p<0.0001). Mucosal healing was established in 12.6% of OZA vs. 3.7% of PBO treated patients (p<0.001).

IP subgroup analyses

Results of prespecified subgroup analyses for the primary endpoint are likely to reflect the difficulties in treating patients with more active disease as indicated by the prior anti-TNF:

- *Subgroup analyses by prior anti-TNF use (yes/no)* did not show significant differences between OZA 1 mg and PBO treated subjects with previous anti-TNF exposure at Week 10 for the primary endpoint clinical remission.
- *Subgroup analyses by corticosteroid use at screening (yes/no)* yielded nominally significantly greater proportions of subjects who achieved the primary endpoint clinical remission with OZA 1 mg as compared to PBO, regardless of corticosteroid use at screening 10 ($p < 0.05$).

IP withdrawals

In Cohort 1, 11.1% of the PBO and 6.5 % of the OZA group in Cohort 1 discontinued from the IP. Lack of efficacy was the most frequently reported reason for discontinuation in the PBO group (4.6%), but was infrequent in the OZA 1 mg treatment group (0.9%). In Cohort 2, the discontinuation rate was 11.7%, mostly due to withdrawal by the subject (5.4%), followed by adverse event (AE) (3.3%) and lack of efficacy (2.5%).

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Response to treatment during IP and continuation in the MP
Similar proportions of subjects treated with OZA 1 mg achieved a clinical response in Cohort 1 (47.8%) and Cohort 2 (52.6%). 93.5 % of the Cohort 1 OZA group, 88.9% of the PBO group and 88.3% of Cohort 2 completed the IP, with continuation into RPC01-3101 MP rates of 54.3%, 31.9% and 61%, and programme discontinuation rates of 2.1%, 1.4% and 5.7%. Overall, 457 subjects in Cohort 1 and Cohort 2 with a clinical response at Week 10 were re-randomised to continue in the MP on OZA 1 mg (N=230) or PBO (N = 227) and contributed to the ITT Population.

MP efficacy results
MP primary endpoint clinical remission
Subjects continuously treated with OZA achieved a highly statistically significant *clinical remission* rate at MP Week 52 compared to subjects re-randomised to PBO (37.0% vs. 18.5%, treatment difference 18.5%, 95% CI 10.8, 26.4; odds ratio 2.755, 95% CI 1.767, 4.294, p<0.0001). Results of all sensitivity analyses were confirmatory.

MP key secondary endpoints
MP key secondary endpoints were all met. Sensitivity analyses for the first secondary endpoint *clinical response* yielded supportive results.

MP subgroup analyses
MP subgroup analyses did not yield differences for the subgroups *prior anti-TNF use (yes/no) or corticosteroid use at Week 10 (yes/no).*

MP discontinuation rates and reasons for withdrawal
Completion rate for the MP was highest in the OZA - OZA group (80.0%), followed by the PBO-PBO (65.2%) and the OZA - PBO (54.6%) groups. The most frequently reported reason for stopping treatment was disease relapse (13.5% in the OZA - OZA arm and 33.9% in the OZA - PBO arm). With LoQ, the agency requested post hoc efficacy analysis for subjects with prior anti-TNF and corticosteroid use at screening. These analyses yielded inferior efficacy for this subgroup with respect to primary and secondary endpoints, thereby reflecting the underlying highly active and more severe disease. However, patients had a chance to profit from longer OZA treatment during maintenance, with almost 19% of subjects achieving clinical remission. Another post hoc comparison of the long-term safety events between subjects treated exclusively with PBO vs. subjects treated exclusively with OZA over 52 weeks requested by the agency did not yield novel AEs associated with OZA therapy.
Overall, the results demonstrate efficacy of Zeposia in achieving and maintaining *clinical remission* during induction and maintenance periods for moderately to severely active UC with prior ineffectiveness of UC treatment.

Key supportive phase 2 study RPC01-202
RPC01-202 is a completed Phase 2, multicentre, randomised, double-blind, treat-through, PBO-controlled parallel-group study to evaluate the clinical efficacy and safety of OZA vs. PBO for moderate to severe UC. Overall, the efficacy results of study RPC01-202 are in line with the results obtained in phase 3 study RPC01-3101.

5.4 Safety

Safety population and pooling
Clinical safety data from three different data pools from OZA Phase 2 and Phase 3 studies were available for safety analysis (labelling in sequence to the existing pools included in the previous multiple sclerosis (MS) submission). Data on subjects with Crohn's disease in ongoing PBO-controlled trials are not included in the pooled data since these data are still blinded. Overall, the AE profile reported for patients treated with OZA 1 mg in the three safety pools was highly similar.

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Pool F Induction
Data from 281 PBO treated and 496 OZA 1 mg treated subjects during the IPs of UC controlled studies RPC01-202 and RPC01-3101 Cohort 1. Mean duration of exposure to OZA 1 mg was 10 weeks in OZA and PBO treated subjects.

RPC01-3101 MP
Data from the randomised withdrawal MP from controlled study RPC01-3101. Mean duration of exposure was longer for the 230 subjects in the OZA - OZA group as compared to the 227 subjects in the OZA - PBO group (~38 weeks versus ~31 weeks).

Pool G
Pool G includes safety data from UC controlled and open-label studies RPC01-202 IP, MP, and Open-label period (OLP), RPC01-3101 IP Cohorts 1 and 2, and MP as well as long-term safety of OZA 1 mg in UC subjects from study RPC01-3102 OLE, including 1158 UC subjects exposed to OZA 1 mg (Pool G) (868 subjects ≥ 6 months, 716 subjects ≥ 12 months, and 322 subjects ≥ 24 months). Mean exposure to OZA 1 mg was 19 months, total cumulative exposure was 1842 subject years (SY). 868 subjects were on OZA ≥ 6 months, 716 ≥ 12 months and 322 ≥ 24 months.

TEAEs
In Pool G (long-term use in UC), the most frequently reported TEAEs (≥ 5% of subjects), which occurred at a ≥ 1% higher incidence compared with PBO, were consistent with the known safety profile of OZA 1 mg (respective preferred terms: lymphopenia, nasopharyngitis, alanine aminotransferase increased, and headache).
Incidences of severe TEAEs and TEAEs leading to temporary interruption of study drug were similar between the treatment groups and low overall. The rate of serious TEAEs was 13% in the OZA 1 mg treated subjects (13.0%) vs. 6.9% of PBO treated subjects. Ulcerative colitis (worsening/flare) represented the most frequently reported serious TEAE in the OZA 1 mg treated group (3.8%) and the PBO group (3.3%). Considering the difference in exposure between the OZA and PBO groups (1922.5 versus 249.2 SY, respectively), the incidence rate (IR) of UC worsening/flare was lower with OZA 1 mg than PBO (IR 23.2 for OZA versus 68.8 for PBO).

Deaths
Over the entire OZA programme including the MS studies, there were 14 deaths in the entire OZA clinical development programme as of 31 Mar 2020 (MS Programme: 10 deaths, UC programme: 3 deaths, Crohn's disease programme: 1 death). Overall, impairment of the immune response led to infections or tumour in 2 of 3 deaths during the UC programme (1 death due to influenza pneumonia in IP Cohort 2 after 6 weeks of OZA 1mg exposure, 1 sudden death of unidentified aetiology after 19 months of OZA 1 mg exposure during RPC01-3102 OLE, 1 death after 32 weeks of OZA 0.5 mg and 863 days of OZA 1 mg exposure in a patient with leukopenia and adenocarcinoma of gastric, pancreatic, biliary or endometrial (intestinal type) origin during RPC01-202 OLP.

Adverse events of special interest (AESI)
Heart rate over the entire OZA programme including the MS studies:
The known problem of bradycardia in the OZA initiation phase could basically be managed by the titration scheme in the UC development programme. Overall, 2 subjects experienced the TEAE of bradycardia on Day 1 of dosing that did not require treatment or action on the study drug. There were no TEAEs of bradycardia in MP RPC01-3101 or during chronic treatment.

Blood pressure
During MP RPC01-3101, subjects on OZA - OZA had a mean increase from baseline in systolic blood pressure of 5.1 mm Hg compared to 1.5 mm Hg in OZA - PBO subjects at Week 52. These findings were highly similar to the systolic blood pressure increase during MS phase 3 studies. In Pool G, hypertensive crisis reported by 2 subjects in the OZA and 1 subject in the PBO group with all subjects having a history of hypertension, recovering without clinical sequelae, and continuing with study drug after the event.

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Hepatic effects
Hepatic enzyme elevations (ALT, AST, GGT) and small increases in mean total bilirubin were seen in UC subjects treated with OZA 1 mg, an AE known from the MS population. These abnormalities were generally asymptomatic, resolved with continued treatment, and did not lead to severe drug-induced liver injury. The majority of subjects with a post-baseline ALT > 3x ULN (approximately 96% of subjects in the controlled and uncontrolled UC studies and 79% of subjects in the two active-controlled Phase 3 MS studies) continued OZA 1 mg treatment, with most values returning to ≤ 3x ULN within approximately 2 to 4 weeks. The discontinuation rate because of elevations in ALT or AST > 5 x ULN was 0.8% of OZA treated subjects in the controlled and uncontrolled UC and 1.1% in the two active-controlled Phase 3 MS studies.

Infections
In RPC01-3101 MP, nasopharyngitis, herpes zoster, oral herpes and gastroenteritis were >1% more frequent in the OZA arm (all ≤ 3%). In Pool G, the IR per 1000 SY in the OZA 1 mg treatment group was higher than the PBO treatment group for nasopharyngitis, bronchitis, herpes zoster, and sinusitis when adjusted for the lower exposure of PBO in Pool G. The rate of TEAEs related to infection leading to discontinuation of study drug in the OZA 1 mg treatment group was 0.6% in the UC programme (0.2% MS programme).

Macular oedema
Optical coherence tomography follow-up was implemented to identify subjects for further ophthalmologic examination in the UC programme. Overall, 5/1158 subjects (all in the OZA 1 mg group, all with pre-existing risk factors and/or comorbid conditions known to cause macular oedema) in Pool G. All were reversible, 3/5 resulted in discontinuation of study drug. Macular oedema rate was 0.3% in the UC OZA group, similar to the incidence in the MS population.
Malignancies: In Pool G, there were 14 malignancies (8/14 non-cutaneous) reported in Pool G with 12 occurring during OZA treatment (6 cutaneous, 6 non-cutaneous malignancies, none occurring in > 1 subject) and two after completion of OZA induction and re-randomisation to PBO and no malignancies suggestive of immunosuppression (i.e., lymphoma). The IR for all malignancies was 6.3 per 1000 SY (estimated background IR per 1000 patient years of any malignancies in IBD patients: ≈7.856 (95% CI: 7.54, 8.185). 3/1666 subjects (0.2%) developed colorectal cancer (CRC) across the UC programme, all with known CRC risk factors (long duration of disease, extensive disease and/or prior use of azathioprine).

Pulmonary effects
Patients with pre-existing pulmonary disease were excluded from UC study participation. FEV1 and FVC were reduced by < 100 ml in the OZA 1 mg group, primarily due to changes during the first 3 months (similar to the findings in the MS programme). There was evidence for reversibility based on RPC01-3101 MP data (return towards baseline values after re-randomisation to PBO). Clinically, respiratory TEAEs in the controlled studies were similar across treatment groups, with no serious TEAEs and one TEAE leading to discontinuation.

Lymphocyte count
In Pool G, 5.3% of patients developed lymphocyte counts < 0.2 x 10^9/L (MS clinical studies 3.3%). Decreases became evident as early as 5 weeks after OZA initiation with sustained reductions throughout the treatment period. In Pool G, the majority of subjects with lymphopenia recovered to ≥ 0.2 x 10^9/L within 2 weeks. Analysis of off-treatment absolute lymphocyte count (ALC) recovery in 325 subjects (exposed to OZA 1mg for ≥ 90 days with ≥1 post baseline on-treatment ALC assessment and ≥ 1 off-treatment ALC assessment) yielded a median time to recovery of ALC to normal levels of 35 days after the last OZA dose.

Safety in special subgroups (all Pool G based)
Subgroup analyses suggested a decreased tolerability in patients ≥ 65 as well as in subjects with prior anti-TNF use. In subjects with corticosteroid use at baseline, the rate of infections (including

nasopharyngitis, upper respiratory tract infection, bronchitis) in OZA treated subjects was increased as compared to subjects with no corticosteroid use at screening.

Further safety issues
Overdose with OZA (> 1 mg/d), rebound and withdrawal effects and use in pregnancy and lactation did not raise any specific concerns.

Class warnings for S1P receptor modulators
These include lymphopenia, immunosuppression, serious infections, progressive multifocal leukoencephalopathy (PML), macular oedema, posterior reversible encephalopathy syndrome (PRES), respiratory effects, increased liver enzymes, increased blood pressure, and malignancies. PRES and PML were not reported in the UC programme.

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Clinical Pharmacology Aspects
Beneficial effects and respective uncertainties
The results of the pop PK analyses for CC112273 and ozanimod were in agreement with the previous analyses. There were no clinically relevant pharmacokinetic differences between healthy subjects, RMS patients and UC patients for both CC112273 and ozanimod. The addition of the UC patients provided pharmacokinetic data in elderly patients, which were previously missing. There were no apparent pharmacokinetic differences compared to younger subjects.
The exposure-response analysis of efficacy in UC patients indicated a difference between placebo and ozanimod treatment.

Unfavourable effects and respective uncertainties
The pharmacokinetic data in elderly subjects were exclusively derived from UC patients. As there were no major pharmacokinetic differences between healthy subjects, RMS patients and UC patients, no dose adjustments in elderly patients are required from a pharmacokinetic point of view. However, no safety and efficacy data are available for elderly RMS patients. This is adequately reflected in the information for healthcare professionals.
There was no clear relationship between CC112273 AUC_{ss} and clinical remission in UC patients. It is unclear from a pharmacometric point of view whether the plateau of a potential exposure-response relationship was reached, or whether the available CC112273 concentration range was too narrow to detect an exposure-response relationship, as only one dose level was investigated.
The risk of experiencing increased ALT/AST values or infections increased with increasing CC112273 exposure. However, the ALT/AST model did not describe the data very well.

Benefit-risk balance
The newly submitted pharmacokinetic data were in agreement with the previous data.

Clinical Aspects
The application for the indication *treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent* was supported by pivotal phase 3 study RPC01-03101 (referred to as RPC01-3101). This study enrolled a population with moderate to severe active UC.
Approximately 30% of subjects had prior exposure to biologic agents (anti-TNFs and anti-integrins), and about 40% had prior exposure to immunomodulators (such as azathioprine and 6-mercaptopurine) and had failed to respond, or were intolerant, to prior treatment. These characteristics are consistent with the UC population addressed in the requested indication.

Benefit
Ozanimod reached the primary endpoint clinical remission with inducing and maintaining clinical remission in a statistically significantly greater proportion of subjects at week 10 (end of IP) as compared to subjects on placebo (18.4% vs. 6.0%; $p < 0.0001$) and at week 52 (end of MP)

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compared to subjects re-randomised to placebo (37.0% vs. 18.5%; p < 0.0001). Subgroup analyses further demonstrated efficacy for the primary endpoint with no respect to the prior use of anti-TNF biologics. Analyses of secondary endpoints were also consistent with the results for the primary endpoint.

Risks

Ozanimod demonstrated an acceptable safety profile and was generally well tolerated with 80% completion rates of the maintenance period of 42 months in the pivotal study. The most common adverse events related to the proposed dose of OZA 1 mg in the UC population corresponded to lymphopenia, hepatic enzyme increases, nasopharyngitis (including pharyngitis and viral respiratory tract infection), as well as herpes zoster and herpes simplex. The UC study programme did not generate new, previously unknown safety signals and confirmed known adverse drug reactions.
The known risk for bradyarrhythmia during the initiation of OZA treatment was manageable under the established dose escalation regimen and first-dose monitoring.
The incidence rate of malignancies reported with ozanimod in the UC programme, including colorectal cancer, did not differ significantly from the expected background rate in the UC and age-matched general population. From the available data so far, it is not evident whether longer exposure to ozanimod could increase colorectal cancer rates in the UC population with their specific need for long-lasting therapy.
Other potential risks of OZA such as e.g. symptomatic bradycardia, severe liver injury, lymphopenia, serious infections including PML, macular oedema, malignancy, PRES, and embryofetal toxicity in exposed pregnant females, are addressed in the information for healthcare professionals.

Overall benefit-risk assessment

Ozanimod at a once daily dose of 1 mg taken orally has demonstrated a favourable benefit-risk profile that supports the proposed indication extension to adult patients with moderate to severe active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Zeposia was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Zeposia®

Composition

Active substances

Ozanimod (as hydrochloride)

Excipients

Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, gelatin, titanium dioxide, iron oxide, printing ink (shellac, propylene glycol, potassium hydroxide, iron oxide).

One hard capsule contains 0.187 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Hard capsules containing 0.23 mg of ozanimod (equivalent to 0.25 mg of ozanimod hydrochloride)

Hard capsules containing 0.46 mg of ozanimod (equivalent to 0.5 mg of ozanimod hydrochloride)

Hard capsules containing 0.92 mg of ozanimod (equivalent to 1.0 mg of ozanimod hydrochloride)

Indications/Uses

Multiple Sclerosis

Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Ulcerative colitis

Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Dosage/Administration

The recommended dose of Zeposia is 0.92 mg orally once a day.

Initiation of treatment

The initial dose escalation regimen of Zeposia shown in Table 1 is required from Day 1 to Day 7. Following the 7-day dose escalation, the dosage is 0.92 mg orally once a day starting on Day 8. Initiation of Zeposia without dose escalation may result in greater reductions in heart rate (see section “Warnings and precautions”).

Zeposia capsules should be swallowed whole and can be administered with or without food.

If a dose of Zeposia is missed, the next scheduled dose should be taken the following day.

Table 1: Dose escalation regimen

Days 1 - 4	0.23 mg once a day
Days 5 - 7	0.46 mg once a day
Days 8 and after this	0.92 mg once a day

Reinitiation of therapy following treatment interruption

The same dose escalation regimen as described in Table 1 is recommended when treatment is interrupted for:

- 1 day or more during the first 14 days of treatment.
- more than 7 consecutive days between Day 15 and Day 28 of treatment.
- more than 14 consecutive days after Day 28 of treatment.

If the interruption of the treatment is of a shorter duration than described above, continue the treatment with the next dose as planned.

Prior to initiation of therapy

Liver function test

The results of a recent (i.e. performed within the last 6 months) liver function test (transaminase and bilirubin levels) are to be obtained (see section “Warnings and precautions”).

Blood count

The results of a recent (i.e. performed within the last 6 months or after discontinuation of prior MS or UC therapy) complete blood count, including the lymphocyte count are to be obtained (see section “Warnings and precautions”).

Cardiac examination

In order to check whether any pre-existing cardiac conduction abnormalities are present, an electrocardiogram (ECG) should be performed and, if necessary, a cardiological opinion obtained. This also applies to patients with other cardiac pre-existing conditions (see section “Warnings and precautions”).

Examination of lung function

UC patients with severe pulmonary disease were not studied. Ozanimod should be used with caution in UC patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary

disease. In patients with severe pulmonary disease (pulmonary fibrosis or chronic obstructive pulmonary disease), pulmonary function testing (e.g., spirometry) should be performed before initiating therapy with Zeposia (see the "Warnings and Precautions" section).

Ophthalmological examination

In patients with a history of diabetes mellitus, uveitis or a retinal disease, an ophthalmological examination of the fundus of the eye including the macula should be performed (see section “Warnings and precautions”).

Current or previous medication

You can find recommendations about patients switching to Zeposia from other disease-modifying treatments and other immunosuppressive or immunomodulating treatmentsor have taken them until recently in "Warnings and precautions: Prior treatment with immunosuppressants or immunomodulating treatments".

Vaccinations

Before initiating treatment with Zeposia, all necessary vaccinations are to be completed in accordance with current vaccination guidelines.

No clinical data are available with regard to the efficacy and safety of vaccinations in patients who are taking Zeposia. Avoid the use of live attenuated vaccines during and for 3 months after treatment with Zeposia.

If live attenuated immunisations are required, the vaccination must be administered at least 1 month before the initiation of Zeposia.

Varicella zoster virus (VZV) vaccination of patients without documented immunity to VZV is recommended at least 1 month prior to initiating treatment with Zeposia. In addition, it is advised to consider the current local vaccination guidelines for vaccination against Varicella zoster virus.

Patients with impaired hepatic function

The pharmacokinetics of ozanimod have not been evaluated in subjects with severe hepatic impairment. Use in patients with severe hepatic impairment (Child-Pugh Class C) is contraindicated (see section “Contraindications”).

There have been no clinically meaningful differences in systemic exposure to ozanimod or its major active metabolite CC112273 in subjects with mild or moderate hepatic impairment (Child-Pugh Classes A and B) compared with their matched healthy subjects. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B).

Patients with impaired renal function

No adjustment of the dose is necessary for patients with renal impairment.

There have been no clinically meaningful differences in systemic exposure to ozanimod or its active metabolites in subjects with end-stage renal disease compared with healthy subjects.

Elderly patients

Limited data are available for RRMS patients > 55 years of age, and > 65 years of age for UC patients. Based on population PK analysis, no dose adjustment is needed in patients over 55 years of age. Caution should be used in RRMS patients > 55 years of age and UC patients over 65 years of age, given the limited data available and potential for an increased risk of adverse reactions particularly Herpes zoster infections in this population, especially with long-term treatment (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Zeposia in paediatric and adolescent patients (<18 years) have not yet been studied.

Contraindications

- Hypersensitivity to ozanimod or any of the excipients.
- Treatment should not be initiated in patients who have experienced myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or Class III/IV heart failure during the last 6 months (see section “Warnings and precautions”).
- Treatment should not be initiated in patients who have a known history or the current presence of second-degree atrioventricular (AV) block Type II or third-degree AV block, sinoatrial block, or sick sinus syndrome, unless the patient has a functioning pacemaker (see section “Warnings and precautions”).
- Treatment should not be initiated in patients with severe untreated sleep apnoea.
- Immunodeficient state (see section “Warnings and precautions”).
- Patients with an increased risk of opportunistic infections, including patients who are currently receiving immunosuppressive treatment or who are immunocompromised (see section “Warnings and precautions”).
- Severe active infections or active chronic infections (hepatitis, tuberculosis) (see section “Warnings and precautions”).
- Active malignancy.
- Severe hepatic impairment (corresponding to Child-Pugh Class C).

- Active macular oedema.
- Pregnancy.

Warnings and precautions

Reduction in Heart Rate

Initiation of treatment with Zeposia

Prior to the initiation of treatment with Zeposia, an ECG is to be performed in all patients in order to establish the presence of any pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first-dose monitoring is recommended (see below).

The initiation of Zeposia may result in transient reductions in the heart rate (HR) (see section "Undesirable effects") and, therefore, the initial dose escalation regimen to reach the dose (0.92 mg) on Day 8 should be followed (see section "Dosage/Administration"). The greatest mean reduction in HR compared with baseline after the initial dose of 0.23 mg of Zeposia was 1.2 beats per minute (bpm) (see "Undersirable effects); this reduction started in Hour 4, with the greatest reduction occurring in Hour 5 of Day 1, and there was a return to near baseline at Hour 6.

Heart rates below 40 beats per minute have not been observed. Initiation of Zeposia without dose escalation may result in greater reductions in the heart rate.

First-dose monitoring in patients with certain pre-existing cardiac conditions

Due to the risk of transient decreases in the heart rate with the initiation of Zeposia, 6-hour monitoring for signs and symptoms of symptomatic bradycardia is recommended after administration of the first dose in the case of patients with a resting heart rate <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure (see section "Contraindications" and "Undesirable effects").

Patients should be monitored by means of hourly pulse and blood pressure measurements during this 6-hour period. An ECG is recommended prior to, and at the end of this 6-hour period.

Additional monitoring is recommended in patients if at hour 6 post-dose:

- heart rate is below 45 bpm;
- heart rate is the lowest value post dose, suggesting that the maximum decrease in HR may not yet have occurred;
- evidence of a new onset second-degree or higher AV block on the 6-hour post-dose ECG
- QTc interval ≥500 msec.

In these cases, appropriate management should be initiated and observation continued until the symptoms/findings have resolved. If medical treatment is required, monitoring should be continued overnight and a 6-hour monitoring period should be repeated after the second dose of Zeposia.

Zeposia was not studied in patients with myocardial infarction (MI), unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation or Class III/IV heart failure during the last 6 months (see section “Contraindications”). The UC clinical development program did not study patients with specific cardiac conduction abnormalities (significant QT prolongation (>450 msec in males and >470 msec in females)) existing risk factors for QT prolongation, or cardiac disease without cardiac consultation.

Cardiologist advice should be obtained prior to the initiation of Zeposia in the following patients in order to decide whether the use of Zeposia can be safely initiated and in order to determine the most appropriate monitoring strategy:

- a history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or a history of recurrent syncope or symptomatic bradycardia;
- pre-existing significant QT interval prolongation (QTcF >450 ms in men and >470 ms in women) or other risks of QT prolongation and treatment with other medicinal products which may potentiate bradycardia;
- treatment with Class Ia antiarrhythmics (e.g. quinidine, disopyramide) or Class III antiarrhythmics (e.g. amiodarone, sotalol) which have been associated with cases of torsades de pointes in patients with bradycardia has not been studied in the case of Zeposia.

Blood pressure effects

In MS and UC controlled clinical studies, hypertension (see Section “Undesirable effects”) has been more frequently reported in patients treated with ozanimod than in patients treated with IFN β-1a IM (MS) or placebo (UC) and in MS and UC patients receiving concomitant ozanimod and SSRIs or SNRIs (see “Interactions” and “In vitro studies”). The blood pressure should be regularly monitored during treatment with ozanimod, and, if necessary, initiate antihypertensive therapy.

Elevated hepatic enzymes

Elevations of aminotransferases may occur in patients who are receiving Zeposia (see section “Undesirable Effects”).

Prior to the initiation of Zeposia, liver function tests (transaminase and bilirubin levels) are to be performed, if no recent results (i.e. from the last 6 months) are available.

If there are no clinical symptoms, the liver transaminase and bilirubin levels should be monitored at Months 1, 3, 6, 9 and 12 during treatment and periodically after this.

If the liver parameters are increased to above 5 fold the Upper Limit of Normal (ULN), the tests should be carried out more frequently, If an increase to above 5 fold the ULN is confirmed, treatment with Zeposia should be interrupted and should only be resumed in the case of normalised liver parameters.

Patients who develop symptoms suggestive of hepatic dysfunction such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia or jaundice and/or dark urine should immediately have their hepatic enzymes checked and Zeposia should be discontinued if significant liver injury is confirmed.

Patients with pre-existing liver disease may be at an increased risk of developing elevated hepatic enzymes when taking Zeposia. Therefore, Zeposia should be used with caution in these patients.

Zeposia has not been studied in patients with severe pre-existing liver damage (Child-Pugh Class C) and in UC patients with an increase in transaminases greater than 2-fold and/or direct bilirubin greater than 1.5-fold of the upper limit. Ozanimod must not be used in patients with severe hepatic impairment (see "Contraindications").

Immunosuppressive effects

Zeposia has an immunosuppressive effect which predisposes patients to the risk of infection, including the risk of opportunistic infections, and it may increase the risk of developing malignancies. Physicians should carefully monitor patientsduring and up to three months after discontinuation of therapy with ozanimod, especially those with concurrent conditions or known factors such as previous immunosuppressive treatment (see Section “Infections”, “Prior and concomitant treatment with antineoplastic,non-corticosteroid immunosuppressive or immune-modulating treatments” and Section “Interactions”). If this risk is suspected, discontinuation of the treatment should be considered by the physician on a case-by-case basis. There are insufficient data to date on the impact of ozanimod on the increased risk of colorectal cancer (CRC) associated with UC.

Infections

Risk of infections

Zeposia causes a mean reduction in the peripheral blood lymphocyte count to approximately 45% of baseline values because of the reversible retention of lymphocytes in lymphoid tissues. Zeposia may, therefore, increase the susceptibility to infections. Zeposia increases the risk of viral respiratory infections, urinary tract infections and herpes infections (see section "Undesirable effects").

A recent (i.e. obtained within the last 6 months or after discontinuation of prior MS or UC therapy) complete blood count, including the lymphocyte count, is to be obtained prior to the initiation of Zeposia.

Periodic assessments of the CBC are also recommended during treatment. Absolute lymphocyte counts <0.2 x 10^9/L, if confirmed, should lead to interruption of Zeposia treatment until the level reaches >0.5 x 10^9/L, when the reinitiation of Zeposia can be considered.

The initiation of Zeposia in patients with an active infection is to be delayed until the infection has been resolved.

If a patient develops a serious infection, interruption of the Zeposia treatment is to be considered.

After discontinuing Zeposia 0.92 mg, the median time taken for peripheral blood lymphocytes to return to the normal range has been approximately 30 days, with approximately 80% to 90% of patients recovering within 3 months (see section “Properties/Effects”).

Because it can take up to 3 months for Zeposia to be eliminated after discontinuation, monitoring for infections is to be continued during this period.

Patients receiving Zeposia should be instructed to report symptoms of infection to their physicians. Effective diagnostic and therapeutic measures should be applied to patients who experience symptoms of infections during treatment.

If progressive multifocal leukoencephalopathy (PML) or a serious opportunistic infection is suspected, the treatment with Zeposia should be suspended until these conditions can be excluded.

Cases of herpes virus infection have been reported in the Zeposia development programme (see “Undesirable effects”). In this development program, patients without a varicella anamnesis (chickenpox) confirmed by a physician and without complete vaccination against varicella zoster virus (VZV) were tested for antibodies to VZV and vaccinated before the initiation of Zeposia. (see subsection "Vaccinations").

Prior and concomitant treatment with antineoplastic,non-corticosteroid immunosuppressive or immune-modulating treatments

In MS and UC clinical studies, patients who have received Zeposia have not been allowed to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies except for corticosteroids used for treatment of MS and UC. The concomitant use of Zeposia with any of these treatments would be expected to increase the risk of immunosuppression and should be avoided. In UC clinical studies, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of ozanimod.

When switching to Zeposia from immunosuppressive medications, the duration of their effects and their mode of action are to be considered in order to avoid unintended additive immunosuppressive effects (see sections “Properties/Effects, Clinical efficacy” and “Interactions”).

In controlled clinical trials with Zeposia, patients who had received alemtuzumab or other immunosuppressants that reduce lymphocyte numbers or inhibit lymphocyte transport were excluded (see also the "Warnings and Precautions" section and section “Dosage/Administration”, “Infections”).

Zeposia can generally be started immediately after the discontinuation of interferons or glatiramer acetate.

Progressive multifocal leukoencephalopathy (PML)

PML is an life-threatening opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) which typically occurs in patients who are immunocompromised and which may lead to death or severe disability.

PML due to JCV infection has been observed in patients treated with S1P receptor modulators including Zeposia and other multiple sclerosis (MS) and ulcerative colitis (UC) therapies.

Known risk factors for PML due to JCV infection include prolonged immunosuppressive therapy, multiple immunosuppressant therapy, or a severely weakened immune system. However, these risk factors do not necessarily have to be present to develop PML.

Typical symptoms associated with PML are diverse, progress over days to weeks and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision and especially neuropsychological/cognitive deficits, such as changes in thinking, memory and orientation which lead to confusion and personality changes. In patients with known multiple sclerosis and new onset of neurological symptoms that do not improve within an expected time frame with appropriate therapy, a differential diagnostic workup for possible PML should be performed promptly.

Physicians should be alert to the possibility of clinical symptoms or MRI findings which may be suggestive of PML. MRI findings may appear before clinical symptoms. If PML is suspected, treatment with Zeposia should be suspended until PML has been excluded.

If PML is confirmed, the treatment with Zeposia should permanently be discontinued. Patients should be informed of the risk of PML before initiating therapy with Zeposia.

Vaccinations

No clinical data are available about the efficacy and safety of vaccinations in patients taking Zeposia. Avoid the use of live attenuated vaccines during and for 3 months after treatment with Zeposia, as they may be less effective and may increase the risk of infection.

If live attenuated vaccine immunisations are required, the vaccination must be administered at least 1 month prior to the initiation of Zeposia.

Varicella zoster virus (VZV) vaccination of patients who have no documented immunity to VZV is recommended at least 1 month prior to the initiation of treatment with Zeposia.

Cutaneous malignant diseases

Half of the neoplasias reported in controlled MS phase 3 studies and in controlled and uncontrolled UC studies with ozanimod have consisted of non-melanoma skin neoplasias (see section “Undesirable effects”).

As there is a potential risk of malignant skin lesions, patients who are treated with ozanimod should avoid unprotected exposure to solar radiation. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Macular oedema

Macular oedema has been observed with Zeposia (see “Undesirable effects”) in patients with pre-existing risk factors or co-morbid conditions.

Patients with a history of uveitis or diabetes mellitus or underlying/co-existing retinal disease are at an increased risk of macular oedema (see “Undesirable Effects”). It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo ophthalmological evaluation of fundus including the macula prior to the initiation of treatment with Zeposia (see “Dosage/Administration, “Prior to initation of therapy”). During treatment with Zeposia, regular ophthalmologic examinations are recommended in patients at increased risk. Such an evaluation is indicated in all patients at any time if there is any change in vision while taking Zeposia.

If macular oedema is confirmed, treatment with Zeposia should be discontinued.

A decision on whether Zeposia should be reinitiated after resolution of the condition needs to take account of the potential benefits and risks to the individual patient. Zeposia has not been studied in patients with a known macular oedema in their history.

Posterior reversible encephalopathy syndrome (PRES)

PRES is a syndrome which is characterised by the sudden onset of severe headache, confusion, cognitive deficits, behavioural abnormalities, neurological symptoms indicative of cortical dysfunction, seizures and visual impairment/loss. Symptoms of PRES are usually reversible, but they may evolve into ischaemic stroke or cerebral haemorrhage.

In controlled MS clinical trials with Zeposia, one case of PRES was reported in a MS-patient in the setting of acute Guillain-Barré syndrome.

If symptoms described above occur during treatment with Zeposia, a comprehensive physical and neurological examination and, if necessary, a cerebral magnetic resonance imaging (MRI) should be performed immediately.

Delayed diagnosis and treatment can lead to chronic consequential damage. If PRES is suspected, the treatment with Zeposia must be discontinued.

Respiratory effects

Ozanimod should be used with caution in patients with severe respiratory disease (pulmonary fibrosis and chronic obstructive pulmonary disease). Before starting and during therapy in patients with severe respiratory disease, lung function should be checked regularly by appropriate methods (e.g. spirometry).

Return of MS disease activity (rebound) after Zeposia discontinuation

Severe disease exacerbation, including a return of disease activity (rebound), has in rare cases been reported after the discontinuation of another S1P receptor modulator in MS. The possibility of severe disease exacerbation after stopping Zeposia treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or the return of a high level of disease activity upon Zeposia discontinuation and appropriate treatment should be instituted as required.

Women of childbearing age

Women of childbearing age should use effective contraception during and until 3 months after discontinuation of therapy with ozanimod (see section "Pregnancy/Lactation").

Co-medications

The joint administration of ozanimod with MAO inhibitors and CYP2C8 inducers (e.g. rifampicin) is not recommended (see section "Interactions").

Other warnings

This medicine contains less than 1 mmol of sodium (23 mg) per capsule; i.e. it is almost “free of sodium”.

Interactions

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites, including the two major active metabolites, CC112273 and CC1084037, and several minor active metabolites such as RP101988 and RP101075. Multiple enzyme systems play an important role in the metabolisation of ozanimod and no single enzyme system determines the overall metabolism of ozanimod.

Effect of ozanimod on other medicinal products

Effects of ozanimod on oral contraceptives

The co-administration of of 0.92 mg of ozanimod once a day and a single dose of oral contraceptive containing 35 µg of ethinyl estradiol (EE) and 1 mg of norethindrone (NE) has not resulted in a change in the exposure to EE or NE. The dosing duration of ozanimod was not long enough for the

active main metabolites to reach steady state. However, CC112273 and CC1084037 do not have an effect on CYP enzymes *in vitro* and so they are not expected to have any effect on the exposure to EE and NE.

Effects of ozanimod on medicinal products which slow the heart rate or atrioventricular conduction (e.g. beta blockers and calcium channel blockers)

In healthy subjects, the initiation of treatment with an initial single dose of 0.23 mg of ozanimod and 80 mg of long-acting propranolol once a day at steady state or 240 mg of diltiazem once a day has not resulted in any additional clinically meaningful changes in heart rate or PR interval compared with either propranolol or diltiazem alone. No data about possible interactions beyond the initiation dose of ozanimod are available.

The administration of ozanimod in patients receiving both a beta blocker as well as a calcium channel blocker has not been studied.

Effects of ozanimod on adrenergic agents

A placebo-controlled crossover study was conducted to assess the potential of Zeposia to enhance pressor responses to pseudoephedrine in healthy subjects. The co-administration of Zeposia with pseudoephedrine did not potentiate the pseudoephedrine-induced blood pressure response. Zeposia increased the pseudoephedrine-induced heart rate response by approximately 3 beats per minute.

Effect of other medicinal products on ozanimod

Inhibitors of the breast cancer resistance protein (BCRP)

Coadministration of ozanimod with cyclosporine, a strong BCRP inhibitor, had no effect on the exposure of ozanimod and its major active metabolites (CC112273 and CC1084037).

Effect of strong inhibitors of CYP2C8

The co-administration of gemfibrozil (a strong inhibitor of CYP2C8) in a dose of 600 mg twice a day at steady state and a single dose of 0.46 mg of ozanimod has not resulted in clinically meaningful changes in ozanimod exposure (AUC), but it has increased the exposure (AUC) to the active metabolites CC112273 and CC1084037 by approximately 47% and 69% respectively. When co-administering ozanimod with strong CYP2C8 inhibitors (e.g. clopidogrel), it is necessary to monitor patients, as there may be a greater risk of adverse reactions.

Effect of strong CYP3A and P-gp inhibitors

The co-administration of itraconazole (a potent inhibitor of CYP3A and P-gp) in a dose of 200 mg once a day at steady state and a single dose of 0.92 mg of ozanimod has not resulted in any clinically meaningful changes in ozanimod, CC112273 or CC1084037 exposure, suggesting that CYP3A makes only a minor contribution to the overall availability of ozanimod.

Effect of strong CYP3A/P-gp and moderate CYP2C8 inducers

The co-administration of rifampicin (a strong inducer of CYP3A and P-gp and a moderate inducer of CYP2C8) in a dose of 600 mg once a day at steady state and a single dose of 0.92 mg of ozanimod has not resulted in any clinically meaningful changes in ozanimod exposure (AUC) and has reduced CC112273 and CC1084037 exposure (AUC) by approximately 60% as a result of CYP2C8 induction, which may result in a reduced clinical response. The co-administration of CYP2C8 inducers (e.g. rifampin) with ozanimod is not recommended.

Monoamine oxidase (MAO) inhibitors

Co-administration with MAO-B inhibitors may decrease CC112273 exposure and consequently also CC1084037 exposure. The potential for clinical interaction with MAO inhibitors has not been studied.

The co-administration of MAO inhibitors (e.g. selegiline, phenelzine) with ozanimod is not recommended.

In vitro studies

Effect of ozanimod and metabolites on CYP enzymes

Ozanimod, CC112273, CC1084037 and other metabolites have no inhibitory effect on the CYPs 1A2, 2B6, 2C19, 2C8, 2C9, 2D6 and 3A and they do not have an induction effect on the CYPs 1A2, 2B6 and 3A.

Effect of ozanimod and metabolites on drug transporters

Ozanimod and its metabolites have no inhibitory effect on the drug transporters P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K or BCRP at clinically relevant concentrations. Therefore, ozanimod administration is not expected to have any effect on the pharmacokinetics of other medicinal products which are substrates of these transporters.

Effect of drug transporter modulators on ozanimod and major active metabolites

In vitro data show that ozanimod may be a substrate of P-gp, but the potent P-gp inhibitor itraconazole has no clinically meaningful effect on ozanimod exposure. *In vitro*, CC112273 is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, MATE1 or MATE2-K. CC1084037 is not a substrate of P-gp, BCRP, OATP1B1 or OATP1B3. The minor active metabolite RP101988 is a substrate of P-qp and BCRP.

Effect of ozanimod on MAO activity

CC112273 and CC1084037 inhibited MAO-B with IC_{50} values of 5.72 nM and 58 nM respectively, showing more than 1’000-fold selectivity over monoaminoxidase (MAO-A) (IC_{50}>1’000 nM). In a serotonergic mouse model study, CC112273 concentrations of up to 84 nM (approximately 4 fold

higher than the mean steady-state C_{max} of CC112273 [19.4 nM] in patients with relapsing MS (RMS) treated with 0.92 mg of ozanimod QD for 12 weeks did not induce signs of serotonin syndrome in normal mice or exacerbate mild serotonin syndrome in mice induced by 5-hydroxytryptophan. In a clinical study with ozanimod, CC112273 and CC1084037 did not have any inhibitory effect on the MAO-B activity of human platelets. In active-controlled MS clinical trials, the use of serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) was not excluded and no patients with serotonin syndrome were identified.

Antineoplastic, immunomodulatory, or immunosuppressive therapies

Switching from Antineoplastic, immunomodulatory, or immunosuppressive therapies to Zeposia

Zeposia has not been studied in combination with antineoplastic, immunomodulatory, or immunosuppressive therapies. Caution should be exercised with concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following cessation of administration of any of these drugs (see section "Warnings and precautions").

When switching disease-modifying therapies, the half-life and mechanism of action of the other therapy must be considered to avoid an additive immune effect while minimizing the risk of disease reactivation (see section "Warnings and Precautions").

No formal studies have been conducted to detect interactions with Zeposia with alemtuzumab. In controlled clinical trial with Zeposia, patients who had recently received alemtuzumab were excluded.

Zeposia may be started immediately after discontinuation of beta-interferon or glatiramer acetate.

Switching from Zeposia to other antineoplastic, immunomodulatory, or immunosuppressive therapies

From pharmacokinetic/pharmacodynamic models with ozanimod, lymphocyte counts returned to normal ranges in 80-90% of healthy subjects within 3 months of discontinuation of therapy (see "Properties/Effects"). In the development program, pharmacodynamic effects, such as a reduction in peripheral lymphocyte count, were found to normalize within 3 months of the last dose of ozanimod.

Pregnancy, lactation

Women of childbearing potential/Contraception in females

Zeposia is contraindicated in women of childbearing potential who do not use effective contraception. Therefore, a negative pregnancy test result must be available and counselling about the risk to the foetus should be provided prior to the initiation of treatment in women of childbearing potential (see section “Pre-clinical data”). Women of childbearing potential should use effective contraception during treatment with Zeposia and for 3 months after the completion of Zeposia treatment.

When stopping Zeposia treatment to plan a pregnancy, the possibility of a return of disease activity should be considered (see section “Warnings and precautions”).

Pregnancy

There are no adequate data on the developmental risk associated with the use of Zeposia in pregnant women. Studies in animals have shown foetotoxicity and teratogenicity (see section “Preclinical data”). Zeposia is contraindicated during pregnancy (see ”Contraindications”) and is not recommended in women of childbearing potential who are not using effective contraception.

Zeposia should be stopped 3 months before planning a pregnancy. If a woman becomes pregnant during treatment, Zeposia must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment.

Lactation

Available pharmacokinetic data in animals have shown excretion of ozanimod/metabolites in milk (see section “Preclinical data”). Physicochemical data suggest the excretion of ozanimod and/or its metabolites in human milk. A risk to newborns/infants cannot be excluded. A decision should be made whether to discontinue nursing or to discontinue the drug.

Fertility

No fertility data are available in humans. In animal studies, no adverse effects on fertility have been observed (see section “Preclinical data”).

Effects on ability to drive and use machines

No studies on the ability to drive or the use of machines have been performed.

Undesirable effects

The adverse drug reactions were determined on the basis of data from the Zeposia clinical development programme. The frequencies of adverse drug reactions correspond to those reported in the Zeposia arms of the controlled MS and UC clinical studies:

In the randomised, controlled clinical MS studies, 1774 patients received Zeposia with an overall exposure of 2’641 person years. The adverse reactions presented are based on safety information from 882 patients treated with 0.92 mg of Zeposia and 885 treated with IFN beta-1a.

In controlled and uncontrolled UC studies, 1158 patients received Zeposia with an overall exposure of 1’842 person years. The adverse reactions presented are based on the safety information from 1158 patients treated with 0.92 mg of Zeposia and 508 patients having received placebo; the mean duration of exposue was 19 months for ozanimod and 5.8 months for placebo.

The most common adverse effects in controlled MS studies were nasopharyngitis (11%), increased alanine aminotransferase levels (5%), and increased gamma-glutamyltransferase levels (5%).

The most common adverse effects in controlled and uncontrolled UC trials (n=1158) were lymphopenia (8.9%), nasopharyngitis (7.4%), anaemia (7.3%), ALT increased (6.2%), lymphocyte

count decreased (6.1%), headache (6%), arthralgia (5.4%), and upper respiratory tract infection (5.1%). The most common adverse reactions leading to discontinuation were related to liver enzyme elevations (1.1%) in the MS clinical studies. The most frequent adverse reactions leading to discontinuation in controlled studies in UC patients (n=1158) were UC worsening (0.8% during induction, none in maintenance) and ALT/hepatic enzyme increased (0.4% in induction and in maintenance).The overall safety profile was similar for patients with MS and UC.

The highest frequency of each of the adverse reactions observed in either the MS or UC studies are given below by organ system and frequency for all adverse reactions in descending order of severity within each frequency group.

The frequencies of the adverse reactions are defined as: very common (≥1/10); common (<1/10, ≥1/100); uncommon (<1/100, ≥1/1000); rare (< 1/1000, ≥ 1/10'000); very rare (< 1/10'000).

Infections and Infestations

Very common: Nasopharyngitis.

Common: Pharyngitis, respiratory tract infection viral, urinary tract infection, Herpes Zoster, Herpes simplex.

Rare: Progressive multifocal leukoencephalopathy (PML).*[1]

*[1] *PML was observed after several years of treatment with Zeposia in the RMS extension study. Frequency data are based on pooled safety data from MS and UC studies.*

Blood and lymphatic system disorders

Very common: Lymphopenia*[2].

*[2] "Very common" is based on pooled data with combined frequency of reports of "lymphopenia" and "lymphocyte count decreased", most cases of which were mild and did not require any dose adjustment.

Immune system disorders

Uncommon: Hypersensitivity (including rash and urticaria).

Nervous system disorders

Common: Headache.

Eye disorders

Uncommon: Macular oedema.*[3]

*[3] *for patients with pre-existing factors.*

Respiratory, thoracic and mediastinal disorders

Common: Pulmonary function test abnormal*[4].

*[4] including pulmonary function test decreased, spirometry abnormal, forced vital capacity decreased, carbon monoxide diffusing capacity decreased, forced expiratory volume decreased.

Cardiac disorders

Common: Bradycardia.

Vascular Disorders

Common: Hypertension, orthostatic hypotension.

Hepatobiliary disorders

Common: Alanine aminotransferase increased[*5], gamma-glutamyltransferase increased[*5], bilirubin increased[*5].

[*5] frequency based on laboratory assessments including all grades.

Skin and subcutaneous tissue disorders

Rare: Basal cell carcinoma, squamous cell carcinoma.

General disorders

Common: Peripheral oedema.

Description of selected undesirable effects

Elevated liver enzymes

In clinical MS studies, ALT increased to ≥ 5 fold the ULN in 1.6% of patients treated with 0.92 mg Zeposia and in 1.3% of patients treated with IFN β-1a IM. Increases of to 3 fold occurred in 5.5% of patients treated with Zeposia and in 3.1% of patients treated with IFN β-1a IM. The median time to 3 fold the ULN was 6 months. The majority (79%) continued the treatment with Zeposia, with the values decreasing to <3 fold the ULN within about 2-4 weeks. Zeposia was discontinued at a confirmed increase of to 5 fold the ULN. Overall, the discontinuation rate due to elevated liver enzymes was 1.1% of MS patients on 0.92 mg of Zeposia and 0.8% of patients on IFN beta-1a IM. No cases of severe drug-induced liver injury have been reported with Zeposia in active-controlled MS clinical trials.

In UC clinical studies, during the 10-week induction period, elevations of ALT to 5-fold the ULN or greater occurred in 0.9% of patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo, and in the maintenance period (42 week i.e. total ozanimod exposure for 52 weeks) elevations occurred in 0.9% and no patients, respectively. In the induction period, elevations of ALT to 3-fold the ULN or greater occurred in 2.6% of UC patients treated with ozanimod 0.92 mg and 0.5% of patients who received placebo, and in the maintenance period elevations occurred in 2.3% and no patients, respectively. Overall, the discontinuation rate due to elevated liver enzyme levels in the controlled UC clinical trials was 0.4% of patients treated with ozanimod at 0.92 mg; there were no discontinuations due to elevated liver enzyme levels in patients receiving placebo.

In controlled and uncontrolled UC clinical studies (n=1158), elevations of ALT to 3-fold and 5 fold of the ULN or greater occurred in 6.0% and 1.7% of patients of UC patients treated with ozanimod 0.92 mg, respectively.

In controlled and uncontrolled UC clinical trials, the majority (96%) of patients with ALT increases greater than 3-fold of the ULN continued treatment with ozanimod, with levels returning to below 3-fold of the ULN within approximately 2 to 4 weeks.

Bradycardia

After the initial dose of Zeposia 0.23 mg, the greatest mean reduction in the HR in a sitting/lying position from baseline occurred at Hour 5 on Day 1 (decrease of 1.2 bpm in the MS clinical studies and 0.7 bpm in the UC clinical studies), returning to near baseline at Hour 6. With continued dose escalation, there were no clinically relevant decreases in the heart rate.

In active-controlled MS clinical trials, bradycardia was reported in 0.5% of patients on Zeposia versus 0% of patients on IFN beta-1a on the day of treatment initiation. After Day 1, the incidence of bradycardia was 0.8% on Zeposia versus 0.7% on IFN beta-1a. Patients who experienced bradycardia were generally asymptomatic. Heart rates below 40 beats per minute were not observed. In MS clinical studies, first-degree atrioventricular block has been reported in 0.6% (5/882) of patients treated with Zeposia versus 0.2% (2/885) patients treated with IFN β-1a IM. Of the cases reported with ozainomd, 0.2% were reported on Day 1 and 0.3% were reported after Day 1. In active-controlled MS clinical trials with dose escalation, second-or third-degree atrioventricular blocks were not reported with Zeposia.

In controlled UC clinical studies, during the induction period, bradycardia was reported on the day of treatment initiation (Day 1), in 0.2% of patients treated with ozanimod and none in patients treated with placebo. After Day 1 bradycardia was reported in 0.2% of patients treated with ozanimod. During the maintenance period, bradycardia was not reported.

Increased blood pressure

In active-controlled MS clinical trials, patients treated with Zeposia had average increases in systolic blood pressure of approximately 1 to 2 mm Hg compared with IFN beta-1a, while no effect on diastolic pressure was observed. The increase in systolic pressure was first detected approximately 3 months after treatment initiation and remained stable throughout the treatment. Adverse effects associated with hypertension (hypertension, essential hypertension and high blood pressure) were reported in 4.5% of patients treated with 0.92 mg of Zeposia 0.92 mg and 2.3% of patients 3 treated with IFN beta-1a.

The mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in UC patients treated with ozanimod is similar to patients with MS. In controlled UC clinical studies, during the 10-week induction period, the average increase from baseline in SBP was 3.7 mm Hg in patients treated with ozanimod and 2.3 mm Hg in patients treated with placebo. During the maintenance period (42 week i.e. total ozanimod exposure for 52 weeks), the average increase from baseline in SBP was 5.1 mm Hg in patients treated with ozanimod and 1.5 mm Hg in patients treated with placebo. There was no effect on DBP. In controlled UC trials, hypertension was reported as an adverse reaction in 1.2% of patients treated with ozanimod 0.92 mg and none in patients treated with placebo in the induction period, and in 2.2% of patients in the maintenance period, respectively. Hypertensive crisis was reported in two patients receiving ozanimod and one patient receiving placebo.

In the pooled controlled and uncontrolled UC studies (n=1158), at 12 months of treatment with ozanimod, the mean change in sitting systolic blood pressure was +5.1 mm Hg and the mean change in sitting diastolic blood pressure was +2.2 mmHg. In controlled and uncontrolled clinical trials in patients with UC (n=1158), hypertension was reported in 3.9% in patients treated with 0.92 mg ozanimod and in 1.0% of patients receiving placebo. In this safety pool, 0.2% of patients had a hypertensive crisis, regardless of receiving ozanimod or placebo.

Blood lymphocyte count reduction

In active-controlled MS clinical trials, 3.3% of patients had lymphocyte counts less than 0.2 x 10^9/L, with values generally resolving to greater than 0.2 x 10^9/L with continued treatment with Zeposia.

In controlled and uncontrolled UC trials (n=1158) 5.3% of patients treated with ozanimod had lymphocyte counts less than 0.2 x 10^9/L, with values generally resolving to greater than 0.2 x 10^9/L with continued treatment with Zeposia.

After discontinuing the 0.92 mg of Zeposia, the median time taken for the peripheral blood lymphocytes to return to the normal range was approximately 30 days, with approximately 80 % to 90% of patients recovering within 3 months.

Infections

In clinical MS studies, the total infection rate (35%) of 0.92 mg of Zeposia was similar to that with IFN β-1a. The overall rate of serious infections was similar between Zeposia (1%) and IFN β-1a IM (0.8%) in clinical MS studies.

In controlled UC clinical studies, during the induction period, the overall rate of infections and rate of serious infections in patients treated with ozanimod were similar to that in patients who received placebo. (9.9% vs. 10.7% and 0.8% vs. 0.4%, respectively). During the maintenance period, the overall rate of infections in patients treated with ozanimod was higher than in patients treated with placebo (23% vs. 12%) and the rate of serious infections was similar (0.9% vs. 1.8%).During the

induction phase, the rate of nasopharyngitis were 3.0% in the ozanimod and 1.1% in the placebo group. During the maintenance phase, the rate of nasopharyngitis was 3.0% and 1.8% in the ozanimod and placebo group, respectively.

In controlled and uncontrolled UC trials (n=1158), 29.1% of patients treated with ozanimod had infections and infestations versus 14.0% in the placebo arms. In this safety pool, 7.4% of patients treated with ozanimod had nasopharyngitis versus 2.0% or patients receiving placebo.

Zeposia increased the risk of upper respiratory tract infections, urinary tract infection, and herpes infections in MS and UC patients.

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Zeposia (see section “Warning and precautions”).

Herpetic infections

In active-controlled MS trials, herpes zoster was reported as an adverse reaction in 0.6% of patients treated with 0.92 mg of Zeposia and in 0.2% of patients on IFN beta-1a.

In controlled and uncontrolled studies UC studies (n=1158), herpes zoster was reported in 2.2% of patients who received ozanimod 0.92 mg and in 0.4% of patients who received placebo. None were serious or disseminated. In this safety pool, 4.6% of ozanimod-treated UC patients ≥ 55 years of age versus 0% in an age-matched control population and 1.8% of ozanimod-treated UC patients < 55 years of age developed herpes zoster (see section “Warnings and Precautions” section).

Respiratory system

Slight dose-dependent reductions in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) have been observed with Zeposia treatment. In Months 3 and 12 of treatment in the clinical MS studies, the median changes in FEV1 (FVC) from baseline in the 0.92 mg of Zeposia group were -0.07 l and -0.1 l (-0.05 l and -0.065 l) with minor changes from baseline in the IFN ß-1a group (FEV1: -0.01 l and -0.04 l; and FVC: 0.00 l and -0.02 l).

Similar to MS clinical studies, small mean reductions in pulmonary function tests have been observed with ozanimod relative to placebo (FEV1 and FVC) during UC clinical studies, in the induction period. There were no further reductions with longer term treatment with ozanimod, in the maintenance period and these small changes in pulmonary function tests were reversible in patients re-randomised to placebo (see section “Warning and Precautions”). Patients with severe pulmonary disease (pulmonary fibrosis, chronic obstructive pulmonary disease) were excluded from study participation.

Cutaneous malignant diseases

In patients treated with ozanimod in MS controlled clinical studies, the most common basal cell carcinomas have occurred with similar incidence rates in the combined ozanimod (0.2%, 3 patients) and IFN ß-1a groups (0.1%, 1 patient).

In controlled and uncontrolled studies UC studies (n=1158), 0.4 % of patients treated with ozanimod had basal cell carcinoma and less than 0.1% patient had squamous cell carcinoma of the skin. There were no cases in patients who received placebo.

Hypersensitivity

Hypersensitivity, including rash and urticaria, has been reported with Zeposia in controlled MS clinical trials at a frequency of uncommon. In UC clinical trials, no case of hypersensitivity was reported.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS (Electronic Vigilance System) portal. You can find information about this at www.swissmedic.ch.

Overdose

Patients should be managed by symptomatic and supportive care in the event of an overdose.

In particular, patients should be examined for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of the heart rate and blood pressure are necessary and an ECG should be performed. Where necessary, a decrease in the heart rate can be treated by the parenteral administration of atropine or isoprenaline.

Properties/Effects

ATC code

L04AA38

Mechanism of action

Ozanimod is a potent sphingosine 1-phosphate receptor modulator, which selectively binds with high affinity to sphingosine 1-phosphate receptors 1 and 5 ($S1P_1$ and $S1P_5$). Ozanimod has minimal or no activity on $S1P_2$, $S1P_3$, and $S1P_4$. *In vitro*, ozanimod and its major active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. The mechanism by which ozanimod exerts its therapeutic effects in multiple sclerosis (MS) and ulcerative colitis (UC) is not known, but it may involve the reduction of lymphocyte migration into the central nervous system and intestine.

The ozanimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Ozanimod has minimal impact on cells involved in innate immune response, which are key components of immunosurveillance.

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites including two major metabolites (See section “Pharmacokinetics2). In humans, approximately 94% of

the total exposure to the circulating active substance is accounted for by ozanimod (6%), CC112273 (73%) and CC1084037 (15%).

Pharmacodynamics

Reduction in peripheral blood lymphocytes

The main pharmacodynamic effect of S1P receptor modulators is an exposure-dependent reduction in the absolute lymphocyte count, which is believed to be an important mechanism in the achievement of the clinical benefit.

In active-controlled MS and UC clinical trials, mean lymphocyte counts decreased to approximately 45% of baseline by 3 months (approximate mean blood lymphocyte counts 0.8 x 10^9/L) and remained stable during treatment with Zeposia.

Reduction in faecal calprotectin (FCP)

In patients with UC, treatment with ozanimod resulted in a decrease in the inflammatory marker, faecal calprotectin (FCP) during the induction period, which was then maintained throughout the maintenance period.

Potential to prolong the QT interval

In a randomised, positive- and placebo-controlled thorough QT study using a 14-day dose escalation regimen of 0.23 mg QD for 4 days, 0.46 mg QD for 3 days, 0.92 mg QD for 3 days, and 1.84 mg QD for 4 days in healthy subjects, no evidence of QTc prolongation was observed as demonstrated by the upper boundary of the 95% one-sided confidence interval (CI), which was below 10 ms. The concentration-QTc analysis for ozanimod and the major active metabolites, CC112273 and CC1084037, using data from another Phase 1 study showed the upper boundary of the 95% CI for the model-derived QTc (corrected for placebo and baseline) to be below 10 ms at maximum concentrations achieved with Zeposia doses >0.92 mg once a day.

Clinical efficacy

Multiple Sclerosis

Zeposia was evaluated in two randomised, double-blind, double-dummy, parallel-group, active-controlled clinical trials of similar design and endpoints in patients with predominantly (98.2%) relapse-remitting MS (RRMS) treated for at least 1 year (Study 1 (SUNBEAM) - Treatment continued for all patients until the last enrolled patient completed 1 year) and 2 years (Study 2 (RADIANCE)).

The doses of Zeposia were 0.92 mg and 0.46 mg given orally once a day, with a starting dose of 0.23 mg on Days 1-4 followed by an escalation to 0.46 mg on Days 5-7 and followed by the assigned dose on Day 8 and after this. The dose of the active comparator, IFN beta-1a, was 30 mcg given intramuscularly (IM) once a week. Both studies included patients who had experienced at least one relapse in the previous year or one relapse in the previous two years with evidence of at least one

gadolinium-enhancing (GdE) lesion in the previous year and who had an Expanded Disability Status Scale (EDSS) score of 0 to 5.0. Neurological evaluations were performed at baseline, every 3 months and at the time of a suspected relapse. MRIs were performed at baseline (Studies 1 and 2), after 6 months (Study 1), after 1 year (Studies 1 and 2) and after 2 years (Study 2).

Patients who were MS treatment naïve or who had received previous MS therapies were eligible for inclusion in the clinical studies. Not eligible for inclusion in the studies were patients who received one of the following MS therapies: lymphocyte trafficking inhibitors (fingolimod, natalizumab), immunosuppresive agents which deplete lymphocytes (e.g. alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone), total body irradiation and bone marrow transplantation.

The primary endpoint of Study 1 and Study 2 was the annualised relapse rate (ARR) over 12 months for Study 1 and over 24 months for Study 2. The key secondary endpoints were: 1) the number of new or enlarging MRI T2 hyperintense lesions over 12 and 24 months 2) the number of MRI T1 GdE lesions on MRI after 12 and 24 months and 3) the time to confirmed disability progression, defined as at least a 1-point increase from baseline EDSS sustained for 12 weeks. Confirmed disability progression was prospectively evaluated in a pooled analysis of Studies 1 and 2. An additional MRI outcome measure was the mean percentage change from baseline in normalised brain volume.

In Study 1, 1’346 patients were randomised to receive 0.92 mg of Zeposia (n = 447), 0.46 mg of Zeposia (n= 451) or IFN beta-1a (n = 448); 94% of patients treated with 0.92 mg of Zeposia, 94% of patients treated with 0.46 mg of Zeposia and 92% of patients treated with IFN beta-1a-completed the study. The mean age was 35.6 years; 66% of patients were female; and the mean time since MS symptom onset was 7 years. The mean EDSS score at baseline was 2.62; 70% had not previously been treated with a disease-modifying therapy. At baseline, the mean number of relapses in the previous year had been 1.3 and 47% of patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 13.6 months.

In Study 2, 1’313 patients were randomised to receive 0.92 mg of Zeposia (n = 433), 0.46 mg of Zeposia (n = 439) or IFN beta-1a (n = 441); 90% of patients treated with 0.92 mg of Zeposia, 85% of patients treated with 0.46 mg of Zeposia and 85% of patients treated with IFN beta-1a-treated patients completed the study. The mean age was 35.5 years; 67% of patients were female; the mean time since MS symptom onset was 6.5 years and the mean EDSS score at baseline was 2.51; and approximately one-third (29%) of the patients had previously been treated with a disease-modifying therapy, predominately interferon or glatiramer acetate. At baseline, the mean number of relapses in the previous year was 1.3 and 43% of the patients had one or more T1 Gd-enhancing lesions (mean 1.7).

The median duration of treatment was 24 months.

The ARR was significantly lower in patients treated with 0.92 mg of ozanimod than in patients who received 30 µg of IFN beta-1a IM. The number of new or enlarging T2 lesions and the number of GdE lesions was significantly lower in patients treated with Zeposia than in patients who received IFN beta-1a.

Three month- and six month-confirmed disability progression were low and similar between Zeposia and IFN beta-1a-treated patients over 2 years. The difference was not statistically significant.

A consistent reduction in the ARR compared with IFN beta-1a was observed in subgroups defined by sex, age, prior DMT therapy and baseline disease activity.

The results for Study 1 and Study 2 are shown in Table 2.

Table 2: Key clinical and MRI endpoints in RMS patients from Study 1 - SUNBEAM and Study 2 - RADIANCE

Endpoints	**Study 1 (SUNBEAM) (≥ 1 year)**		**Study 2 (RADIANCE) (2 year)**	
	Zeposia 0.92 mg (n=447) %	**IFN β-1a IM 30 mcg (n=448) %**	**Zeposia 0.92 mg (n=433) %**	**IFN β-1a IM 30 mcg (n=441) %**
Clinical endpoints				
Annualised relapse rate (primary endpoint)	0.181[a]	0.350 [a]	0.172	0.276
Relative reduction	48% (p<0.0001)		38% (p<0.0001)	
Proportion relapse-free Kaplan-Meier estimate [b]	78% 0.781 (p=0.0002)[c]	66% 0.663	76% 0.756 (p=0.0012)[c]	64% 0.642
Proportion of patients with 3-Month confirmed disability progression (CDP)[d] Hazard ratio (95% CI)	7.6% Zeposia vs. 7.8% IFN β-1a IM 0.95 (0.679, 1.330) p=07651			
Proportion of patients with 6-Month confirmed disability progression (CDP)[d] Hazard ratio (95% CI)	5.8% Zeposia vs. 4.0% IFN β-1a IM 1.413 (0.922-2.165) p=0.1126			
MRI endpoints				
Mean number of new or enlarging T2 hyperintense lesions per MRI[e]	1.465	2.836	1.835	3.183
Relative reduction	48% (p<0.0001)		42% (p<0.0001)	
Mean number of T1 Gd enhancing lesions[f]	0.160	0.433	0.176	0.373
Relative reduction	63% (p<0.0001)		53% (p=0.0006)	

[a] Through the treatment period (mean duration 13.6 months).

[b] Over treatment period for Study 1 and over 24 months for Study 2.

[c] Based on log rank test.

[d] Disability progression defined as 1-point increase in Expanded Disability Status Scale (EDSS) confirmed 3 months or 6 months later.

[e] Over 12 months for Study 1 and over 24 months for Study 2.

[f] At the end of the treatment duration for each study i.e. at 12 months for Study 1 and at 24 months for Study 2.

In Studies 1 and 2, treatment with Zeposia 0.92 mg resulted in reductions in mean percentage change (loss) from baseline in normalised brain volume compared with IFN beta-1a IM (-0.41% versus -0.61% and -0.71% versus -0.94% respectively, nominal p-value <0.0001 for both studies).

Patients who completed the 12- and 24-month main studies were able to enter an open label extension [OLE] study (Study 3 - DAYBREAK) and receive 0.92 mg of Zeposia. Of 760 patients initially randomised to 0.92 mg of Zeposia who entered Study 3, there was a mean cumulative exposure of approximately 3 years. In these patients, the ARR was 0.148 over the cumulative treatment period.

Ulcerative colitis (UC)

The efficacy and safety of ozanimod were evaluated in two multicenter, randomised, double-blind, placebo-controlled clinical studies [TRUENORTH-I (induction period) and TRUENORTH-M (maintenance period)] in adult patients with moderately to severely active ulcerative colitis. TRUENORTH-I included patients who were randomised 2:1 to ozanimod 0.92 mg or placebo. The 10-week induction period (TRUENORTH-I) was followed by a 42-week, randomised, withdrawal maintenance period (TRUENORTH-M) for a total of 52 weeks of therapy. Patients could have had an inadequate response, loss of response, or intolerance to a biologic (e.g., TNF blocker and/or vedolizumab), corticosteroids, and/or immunomodulators (e.g. 6-mercaptopurine and azathioprine) therapy. Patients who had previously failed to respond primarily to at least two biologics were excluded from study participation.

Disease severity assessment was based on the Mayo score, which ranges from 0 to 12 and has four subscores from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (week 0) as a Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥ 2. An endoscopy score of 2 was defined by marked erythema, lack of vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration.

TRUENORTH-I (induction study)

In TRUENORTH-I, patients were randomised to either ozanimod 0.92 mg given orally once daily (n=429) or placebo (n=216) beginning with a dose titration (see section dosage and administration). Patients received concomitant aminosalicylates (e.g., mesalazine 71%; sulfasalazine 13%) and/or oral corticosteroids (33%) at a stable dose prior to and during the induction period.

There were 30% of patients who previously had an inadequate response, loss of response or intolerant to TNF blockers. Of these patients, 63% received at least two or more biologics including TNF blockers; 47% received an integrin receptor blocker (e.g. vedolizumab); 36% failed to ever respond to at least one TNF blocker; 65% lost response to a TNF blocker. There were 41% of

patients who failed and/or were intolerant to immunomodulators. At baseline, patients had a median Mayo score of 9, with 65% of patients less than or equal to 9 and 35% having greater than 9. Patients with a history of primary nonresponse to two or more biologics were excluded from study participation.

The primary endpoint was clinical remission at week 10, defined as a Three-component Mayo: rectal bleeding subscore = 0, stool frequency subscore ≤ 1 (and a decrease of ≥ 1 point from the Baseline Stool Frequency subscore) and endoscopy subscore ≤ 1. Key secondary endpoints at week 10 were clinical response, dendoscopic improvement, and mucosal healing. Clinical response with a definition of Three-component Mayo: A reduction from Baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from Baseline in the Rectal Bleeding subscore of ≥ 1 point or an absolute Rectal Bleeding subscore of ≤ 1 point, endoscopic improvement with a definition of Endoscopy subscore of ≤ 1 point, and mucosal healing defined as Endoscopy subscore of ≤ 1 point and a Geboes index score < 2.0.

A significantly greater proportion of patients treated with ozanimod achieved clinical remission clinical remission and response, endoscopic improvement, and mucosal healing compared to placebo at week 10 as shown in Table 3.

Table 3: Proportion of patients meeting efficacy endpoints in the induction period from TRUENORTH-I (at week 10)

	Ozanimod 0.92 mg (N=429)[f]		**Placebo (N=216)[f]**		**Treatment Difference %[a] (95% CI)**
	n	**%**	**n**	**%**	
Clinical remission[b]	79	18%	13	6%	12% (7.5, 17.2)[f]
Without prior TNF blocker exposure	66/299	22%	10/151	7%	
Prior TNF blocker exposure	13/130	10%	3/65	5%	
Clinical response[c]	205	48%	56	26%	22% (14.4, 29.3)[f]
Endoscopic improvement[d]	117	27%	25	12%	16% (9.7, 21.7)[f]
Mucosal healing[e]	54	13%	8	4%	9% (4.9, 12.9)[g]

CI = confidence interval; TNF = tumor necrosis factor.
[a] Treatment difference (adjusted for stratification factors of prior TNF blocker exposure and corticosteroid use at baseline).
[b] Clinical remission is defined as: RBS = 0, SFS ≤ 1 (and a decrease of ≥ 1 point from the baseline SFS), and endoscopy subscore ≤ 1 without friability.
[c] Clinical response is defined as a reduction from baseline in the 9-point Mayo score of ≥ 2 and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 or an absolute RBS of ≤ 1.
[d] Endoscopic improvement is defined as a Mayo endoscopic score ≤ 1 without friability.
[e] Endoscopic improvement with histologic remission defined as both Mayo endoscopic score ≤ 1 without friability and histological remission (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation Geboes index score < 2.0).
[f] p=<0.0001.
[g] p=<0.001.

TRUENORTH-M (maintenance study)

In order to be randomised to treatment in the maintenance study (TRUENORTH-M), patients had to have received ozanimod 0.92 mg and be in clinical response at week 10 of the induction period.

Patients could have come from either TRUENORTH-I or from a group who received ozanimod 0.92 mg open-label. Patients were re-randomised in a double-blinded fashion (1:1) to receive either ozanimod 0.92 mg (n=230) or placebo (n=227) for 42 weeks. The total study duration was 52 weeks, including both the induction and maintenance periods. Efficacy assessments were at week 52. Concomitant aminosalicylates were required to remain stable through week 52. Patients on concomitant corticosteroids were to taper their dose upon entering the maintenance period.

At study entry, 35% of patients were in clinical remission, 29% of patients were on corticosteroids and 31% of patients who were previously treated with TNF blockers.

As shown in the Table 4, the primary endpoint was the proportion of patients in clinical remission at week 52. Key secondary endpoints at week 52 were the proportion of patients with clinical response, endoscopic improvement, the proportion of patients maintaining clinical remission at week 52, corticosteroid-free clinical remission, mucosal healing and durable clinical remission among patients who achieved clinical remission at 10 weeks of the induction period.

Table 4: Proportion of patients meeting efficacy endpoints in the maintenance period in TRUENORTH-M (at week 52)

	Ozanimod 0.92 mg[a] (N=230)		**Placebo[a] (N=227)**		**Treatment difference %[b] (95% CI)**
	n	**%**	**n**	**%**	
Clinical remission[c]	85	37%	42	19%	19% (10.8, 26.4)[i]
Without prior TNF blocker exposure	63/154	41%	35/158	22%	
Prior TNF blocker exposure	22/76	29%	7/69	10%	
Clinical response[d]	138	60%	93	41%	19% (10.4, 28.0)[i]
Endoscopic improvement[e]	105	46%	60	26%	19% (11.0, 27.7)[j]
Maintenance of clinical remission at week 52 in the subset of patients in remission at week 10[f]	41/79	52%	22/75	29%	24% (9.1, 38.6)[k]
Corticosteroid-free clinical remission[g]	73	32%	38	17%	15% (7.8, 22.6)[j]
Mucosal healing[h]	68	30%	32	14%	16% (8.2, 22.9)[j]
Durable clinical remission[h]	41	18%	22	10%	8% (2.8, 13.6)[l]

CI = confidence interval; TNF = tumor necrosis factor.
[a] Treatment difference (adjusted for stratification factors of clinical remission and concomitant corticosteroid use at week 10).
[b] Clinical remission is defined as: RBS = 0 point and SFS ≤ 1 point (and a decrease of ≥ 1 point from the baseline SFS) and endoscopy subscore ≤ 1 point without friability.
[c] Clinical response is defined as: A reduction from baseline in the 9-point Mayo score of ≥ 2 points and ≥ 35%, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.
[d] Endoscopic improvement is defined as: Endoscopy subscore of ≤ 1 point without friability.

[e] Maintenance of remission defined as clinical remission at week 52 in the subset of patients in clinical remission at week 10.
[f] Corticosteroid-free remission is defined as clinical remission at week 52 while off corticosteroids for ≥ 12 weeks.
[g] Mucosal healing is defined as both Mayo endoscopic score ≤ 1 without friability and histological remission (defined as no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation Geboes index score < 2.0)
[h] Durable clinical remission is defined as clinical remission at week 10 and at week 52 in all subjects who entered the maintenance period.
[i] p=<0.0001.
[j] p=<0.001.
[k] p=0.0025.
[l] p=0.0030

Pharmacokinetics

Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites, including two major active metabolites, CC112273 and CC1084037, with similar activity and selectivity for $S1P_1$ and $S1P_5$ to the parent drug. The maximum plasma concentration (C_{max}) and area under the curve (AUC) for ozanimod, CC112273 and CC1084037 increased proportionally over the dose range of Zeposia of 0.46 mg to 0.92 mg (0.5 to 1 fold the recommended dose).

Following multiple dosing, approximately 94% of the circulating total active drug exposure is accounted for by ozanimod (6%), CC112273 (73%) and CC1084037 (15%).

At an oral dose of 0.92 mg orally once a day in RRMS patients, the geometric mean [coefficient of variation (CV%)] C_{max} and $AUC_{0\text{-}24h}$ at steady state were 231.6 pg/mL (37.2%) and 4’223 pg*h/mL (37.7%) respectively, for ozanimod and 6’378 pg/mL (48.4%) and 132’861 pg*h/mL (45.6%) respectively for CC112273. The C_{max} and $AUC_{0\text{-}24h}$ for CC1084037 are approximately 20% of those for CC112273.

Factors affecting CC112273 are also applicable for CC1084037, as they are interconverting metabolites. Population pharmacokinetic analysis indicated that there were no meaningful differences in these pharmacokinetic parameters in patients with relapsing MS or UC.

Absorption

Following oral administration, the median time to maximum plasma concentration (T_{max}) of ozanimod was approximately 6 to 8 hours. Food intake (high- and low-fat meals) did not alter ozanimod exposure. Food is not expected to have an effect on the metabolism or elimination of metabolites since food only affects the absorption of the parent drug. Thus, ozanimod can be administered with or without food.

Distribution

The mean (CV%) apparent volume of distribution of ozanimod (Vz/F) was 5’590 L (27%), indicating extensive tissue distribution. Binding of ozanimod, CC112273 and CC1084037 to human plasma proteins is high at approximately 98.2%, 99.8%, and 99.3%, respectively.

Metabolism

Ozanimod was extensively metabolized in humans with a number of metabolites identified in plasma, urine and feces. Multiple enzyme systems play an important role in the metabolism of ozanimod and

no single enzyme system predominates in the overall metabolism of ozanimod. The oxidative pathway to formation of carboxylate metabolite RP101988 is mediated by ALDH/ADH while formation of RP101075 by dealkylation is predominantly carried out by CYP3A4. RP101075 is N-acetylated by NAT-2 to form RP101442 or deaminated by MAO-B to form the major metabolite CC112273.

CC112273 is either reduced to form CC1084037 or undergoes CYP2C8 mediated oxidation to form RP101509. CC1084037 is oxidized rapidly to form CC112273 by AKR 1C1/1C2, and/or 3β- and 11β-HSD and undergoes reversible metabolisation to CC112273. The oxido-reduction interconversion between CC112273 and CC1084037 favours the formation of CC112273 and there are no direct metabolites of CC1084037 other than its metabolisation to CC112273 and its subsequent elimination via that pathway. *In vivo*, gut microbial flora plays an important role in the formation of many inactive metabolites via anaerobic reductive metabolism of the oxadiazole ring system.

Elimination

The mean (CV%) oral clearance for ozanimod was approximately 192 L/h (37%). The mean (CV%) plasma half-life ($t_{1/2}$) of ozanimod was approximately 21 hours (15%). Steady state for ozanimod was achieved within 7 days, with an estimated accumulation ratio following repeated oral administration of 0.92 mg once a day of approximately 2.

The model-based mean (CV%) effective half-life ($t_{1/2}$) of CC112273 was approximately 11 days (104%) in RMS patients, with a mean (CV%) time to steady state of approximately 45 days (45%) and an accumulation ratio of approximately 16 (101%). Plasma levels of CC112273 and its direct, interconverting metabolite CC1084037 declined in parallel in the terminal phase, yielding a similar $t_{1/2}$ for both metabolites. Steady state attainment and accumulation ratios for CC1084037 are expected to be similar to CC112273.

Following a single oral 0.92 mg dose of [^{14}C]-ozanimod, approximately 26% and 37% of the radioactivity was recovered from urine and faeces respectively and it was primarily composed of inactive metabolites. The concentrations of ozanimod, CC112273 and CC1084037 in the urine were negligible, indicating that renal clearance is not an important excretion pathway for ozanimod, CC112273 or CC1084037.

Kinetics in specific patient groups

Hepatic impairment

In a dedicated hepatic impairment trial, the exposures (AUC_{last}) for ozanimod and CC112273 were approximately 11% lower and 31% lower respectively in subjects with mild hepatic impairment (Child-Pugh A; N=8) when compared with subjects with normal hepatic function (N=7) following a single oral dose of 0.23 mg of ozanimod. Exposures (AUC_{last}) for ozanimod and CC112273 were approximately 27% higher and 33% lower respectively in subjects with moderate hepatic impairment (Child-Pugh B; N=8) when compared with subjects with normal hepatic function (N=8). These differences were not

considered clinically meaningful. The pharmacokinetics of ozanimod were not evaluated in patients with severe hepatic impairment.

Renal impairment

In a dedicated renal impairment trial, exposures (AUC_{last}) for ozanimod and CC112273 were approximately 27% higher and 23% lower respectively in patients with end-stage renal disease (N=8) compared to subjects with normal renal function (N=8). following a single oral dose of 0.23 mg ozanimod Based on this trial, renal impairment had no clinically important effects on pharmacokinetics of ozanimod or CC112273.

Elderly patients

Population pharmacokinetic analysis showed that steady state exposure (AUC) of CC112273 in UC patients over 65 years of age were approximately 3 - 4% greater than patients 45 – 65 years of age and 27% greater than adult patients under 45 years of age. There is not a meaningful difference in the pharmacokinetics in elderly patients.

Children and adolescents

No data are available regarding the administration of Zeposia to paediatric or adolescent patients (<18 years of age).

Gender

While the population pharmacokinetics of ozanimod are not affected by gender, CC112273 steady-state exposure (AUC) was 35% lower in males than in females. The effect of gender on CC112273 exposure was not considered to be clinically meaningful.

Smoking

Population pharmacokinetic results showed that CC112273 steady-state exposure (AUC) was 50% lower in smokers than in non-smokers. The clinical effects of smoking on ozanimod treatment for patients with RRMS is not known.

Preclinical data

In general toxicology studies conducted in rats (26 weeks) and monkeys (39 weeks), ozanimod produced lymphopenia which was similar to the decreases in lymphocytes observed in humans. In these studies, ozanimod increased lung weights and increased the incidence of mononuclear alveolar infiltrates. Ozanimod administration to rats also had an inhibitory effect on T-cell-dependent IgG and IgM antibody responses.

At the no observed adverse effect levels (NOAELs) in chronic toxicity studies, systemic exposures to the disproportionate main active and persistent human metabolites CC112273 and CC1084037 (see section 5.2), and even to the total human active drug (ozanimod combined with the mentioned

metabolites), were lower than those expected in patients at the maximum human dose of 0.92 mg ozanimod.

Mutagenicity

Overall, ozanimod and main metabolites do not exhibit any *in vitro* or *in vivo* genotoxicity concerns.

Carcinogenicity

Ozanimod was evaluated for carcinogenicity in the 6-month Tg.rasH2 mouse bioassay and the two-year rat bioassay.

In the two-year rat bioassay, no treatment-related tumors were present at any ozanimod dose (up to 19 fold above the recommended human equivalent dose (RHED)). However, exposures of metabolites at the highest dose tested were 62% (CC112273) and 18% (CC1084037) of human exposures at the maximum clinical dose of 0.92 mg ozanimod.

In the 6-month Tg.rasH2 mouse study, a dose-related statistically significant increase in haemangiosarcomas was observed from the lowest dose. Haemangiosarcomas in mice treated with $S1P_1$ agonists are thought to be species specific and not predictive of a risk in humans. At the lowest dose, the total ozanimod exposure was 1’680-fold, that of CC112273 was 2.95 fold and that of CC1084037 was 1.4 fold human exposure at a clinical dose of 0.92 mg of ozanimod.

No other treatment-related tumors were present at any dose in the Tg.rasH2 mouse study.

Reproductive toxicity

Fertility was examined in male and female rats dosed for two weeks prior to and during mating. No effects on fertility were present at the highest dose tested. Exposure multiples (AUC_{0-24}) were 2’550 fold for ozanimod, 14.7 fold for CC112273 and 3.08 fold for CC1084037.

In reproductive toxicity studies, foetal toxicity was observed in rats and rabbits during embryogenesis. The manifestations of oetal toxicity included embryo-foetal death, abnormal and delayed ossification, visceral abnormalities and malformations of the major blood vessels. The cumulative exposure multiples (AUC_{0-24}) of the active substances were below 4 (for the NOAEL in the rat) and below 1 (for the rabbit).

Pre- and post-natal development were not affected by ozanimod administration in rats up to the highest dose tested (2 mg/kg/day). The rat NOAEL exposure margins (AUC_{0-24}) were 90.2 fold for ozanimod and they were below 1 for both metabolites (CC112273 and CC1084037).

Ozanimod and its metabolites were detected in rat milk.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 25°C. Keep out of the reach of children.

Authorisation number

67046 (Swissmedic)

Packs

Zeposia 0.23 mg/0.46 mg: 7 hard capsules (4 x 0.23 mg, 3 x 0.46 mg) initiation pack (B)

Zeposia 0.92 mg: 28 hard capsules (B)

Marketing authorisation holder

Bristol-Myers Squibb SA, Steinhausen

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