Hepatic safety of ozanimod in ulcerative colitis and relapsing multiple sclerosis phase 3 trials

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Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_5$, induces S1P receptor internalization and prevents lymphocyte migration to the intestines[1-3]
- Ozanimod is approved in the United States and European Union for the treatment of moderately to severely active ulcerative colitis (UC) and relapsing forms of multiple sclerosis (MS)[2,3]
- The phase 3 True North trial (NCT02435992) demonstrated the efficacy and tolerability of ozanimod in patients with moderately to severely active UC[4]
- In the phase 3 SUNBEAM (NCT02294058) and RADIANCE (NCT02047734) trials, ozanimod was more effective than interferon beta-1a (IFN ß-1a) and was generally well tolerated in patients with relapsing MS[5,6]
- Other S1P receptor modulators have shown elevations in hepatic enzymes[7-9]
  - Therefore, hepatic enzymes and hepatic-related treatment-emergent adverse events (TEAEs) were closely monitored in the ozanimod clinical trials

Objective

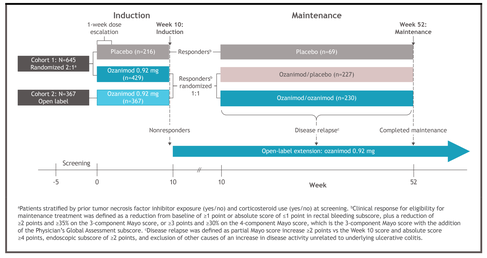
- To evaluate the hepatic safety of ozanimod 0.92 mg in the UC and MS phase 3 clinical trials

Methods

Study design and patients

- The UC trial (True North)[4] was a 52-week, randomized, double-blind, placebo-controlled phase 3 trial that evaluated the efficacy and safety of ozanimod in patients with moderately to severely active UC (**Figure 1**)
- This safety analysis included 216 patients treated with placebo and 796 patients treated with ozanimod 0.92 mg (equivalent to ozanimod HCl 1 mg)

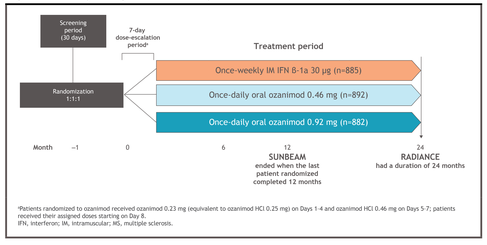
Figure 1. Study design of UC trial (True North)



[a]Patients stratified by prior tumor necrosis factor inhibitor exposure (yes/no) and corticosteroid use (yes/no) at screening. [b]Clinical response for eligibility for maintenance treatment was defined as a reduction from baseline of ≥1 point or absolute score of ≤1 point in rectal bleeding subscore, plus a reduction of ≥2 points and ≥35% on the 3-component Mayo score, or ≥3 points and ≥30% on the 4-component Mayo score, which is the 3-component Mayo score with the addition of the Physician's Global Assessment subscore. [c]Disease relapse was defined as partial Mayo score increase ≥2 points vs the Week 10 score and absolute score ≥4 points, endoscopic subscore of ≥2 points, and exclusion of other causes of an increase in disease activity unrelated to underlying ulcerative colitis.

- The MS trials (SUNBEAM[5] and RADIANCE[6]) were both randomized, double-dummy, active-control phase 3 trials that compared ozanimod 0.92 mg or ozanimod 0.46 mg (equivalent to ozanimod HCl 0.5 mg) with IFN ß-1a 30 µg in patients with relapsing MS (**Figure 2**)
- This safety analysis included 882 patients treated with ozanimod 0.92 mg and 885 patients treated with IFN ß-1a

Figure 2. Study design of MS trials (SUNBEAM and RADIANCE)



[a]Patients randomized to ozanimod received ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on Days 1-4 and ozanimod HCl 0.46 mg on Days 5-7; patients received their assigned doses starting on Day 8.
IFN, interferon; IM, intramuscular; MS, multiple sclerosis.

The incidences of hepatic TEAEs were similar between treatment groups; there were relatively few hepatic-related events (ie, generally asymptomatic laboratory abnormalities) leading to ozanimod discontinuation

Table 3. Incidences of hepatic TEAEs of interest

System organ class[a] Preferred term	UC (True North) Placebo (n=216)	UC (True North) Ozanimod 0.92 mg (n=796)	MS (SUNBEAM/RADIANCE) IFN ß-1a 30 µg (n=885)	MS (SUNBEAM/RADIANCE) Ozanimod 0.92 mg (n=882)
Hepatobiliary disorders[b]	2 (0.9)	3 (0.4)	10 (1.1)	15 (1.7)
Hepatic steatosis	1 (0.5)	0	1 (0.1)	1 (0.1)
Cholelithiasis	0	0	2 (0.2)	1 (0.1)
Steatohepatitis	0	1 (0.1)[c]	0	1 (0.1)
Cholecystitis	0	0	1 (0.1)[d]	1 (0.1)[d]
Hyperbilirubinemia	0	1 (0.1)	1 (0.1)	3 (0.3)
Hepatobiliary disease	0	1 (0.1)	0	0
Hypertransaminasemia	0	0	1 (0.1)	1 (0.1)
Hepatitis toxic[e]	0	0	1 (0.1)	2 (0.2)
Cholangitis sclerosing	1 (0.5)	0	0	0
Gallbladder cholesterolosis	1 (0.5)	0	0	0
Investigations[b]				
ALT increased	0	27 (3.4)	28 (3.2)	47 (5.3)
GGT increased	0	18 (2.3)	11 (1.2)	40 (4.5)
AST increased	0	7 (0.9)	17 (1.9)	16 (1.8)
Liver function test increased	0	6 (0.8)	2 (0.2)	5 (0.6)
Hepatic enzyme increased	1 (0.5)	6 (0.8)	6 (0.7)	12 (1.4)
Blood alkaline phosphatase increased	0	2 (0.3)	0	4 (0.5)
Transaminases increased	0	2 (0.3)	5 (0.6)	2 (0.2)
Blood bilirubin increased	0	1 (0.1)	1 (0.1)	7 (0.8)

[a]Coded using MedDRA, version 22.1. [b]Not all hepatobiliary disorders or investigations are listed, and patients could have reported ≥1 TEAE. [c]Nonalcoholic steatohepatitis. [d]Chronic cholecystitis. [e]All were nonserious and led to discontinuation of ozanimod 0.92 mg in 1 patient.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

Table 4. Hepatic-related TEAEs leading to ozanimod 0.92 mg discontinuation[a]

TEAEs leading to study treatment discontinuation, n (%)	UC (True North) Placebo (n=216)	UC (True North) Ozanimod 0.92 mg (n=796)
Investigations	0	4 (0.5)
ALT increased	0	2 (0.3)
Hepatic enzyme increased	0	1 (0.1)
GGT increased	0	1 (0.1)
LFT increased	0	1 (0.1)
TEAEs leading to study treatment discontinuation, n (%)	**MS (SUNBEAM/RADIANCE) IFN ß-1a 30 µg (n=885)**	**MS (SUNBEAM/RADIANCE) Ozanimod 0.92 mg (n=882)**
Hepatobiliary disorders	0	2 (0.2)
Hepatitis toxic	0	1 (0.1)
Hypertransaminasemia	0	1 (0.1)
Investigations	7 (0.8)	9 (1.0)
ALT increased	3 (0.3)	4 (0.5)
GGT increased	0	2 (0.2)
Abnormal LFT	2 (0.2)	1 (0.1)
AST increased	2 (0.2)	1 (0.1)
Blood bilirubin increased	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	1 (0.1)
Transaminases increased	0	1 (0.1)

[a]One patient may have reported ≥1 TEAE.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IFN, interferon; LFT, liver function test; MS, multiple sclerosis; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

- Key hepatic-related exclusion criteria for the UC and MS trials:
  - Clinically relevant hepatic disease, recurrent/chronic infection (eg, hepatitis A, B, or C virus), or history of alcohol abuse within 1 year prior to randomization
  - Liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x upper limit of normal (ULN) for the UC trial or >1.5 x ULN for the MS trials
  - Persisting elevations of direct bilirubin levels >1.5 x ULN

Study procedures

- Liver function tests (LFTs) were assessed as follows:
  - UC (True North): baseline and Weeks 5, 10, 18, 28, 40, and 52
  - MS (SUNBEAM/RADIANCE): baseline, Month 1, Month 3, and every 3 months thereafter
- In the UC and MS trials, patients with elevations in LFTs (ie, ALT and/or AST) ≥3 x ULN retested their LFT levels <14 days after the original test
  - Upon confirmation of elevation in LFTs, retests were performed weekly until elevated LFTs <3 x ULN or discontinuation criteria for laboratory abnormalities were met
- If LFT elevations had no apparent alternative cause, ozanimod was permanently discontinued as follows:
  - UC (True North):
    - ALT or AST >8 x ULN, ALT or AST >5 x ULN with confirmation within 2 weeks, or ALT or AST >3 x ULN and total bilirubin >2 x ULN
    - ALT or AST >3 x ULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophils >5%
  - MS (SUNBEAM/RADIANCE):
    - ALT or AST >5 x ULN with confirmation of elevation via retest within 2 weeks
- In the UC and MS trials, a hepatic advisory board consisting of unblinded drug-induced liver injury (DILI) advisors reviewed cases of potential clinical significance
  - Drugs can potentially cause severe DILI if they induce elevations that meet Hy's law criteria: ALT or AST ≥3 x ULN and bilirubin >2 x ULN without cholestasis or other explanation (eg, viral hepatitis, preexisting or acute liver disease, another drug causing the liver injury)[10]
- This analysis primarily focused on drug-induced hepatocellular injury data, which are characterized by serum elevations in ALT and AST, rather than drug-induced hepatobiliary injury data, which are characterized by elevations in alkaline phosphatase[11]

Patients

- Baseline patient demographics and clinical characteristics in the UC and MS trials were similar between ozanimod 0.92 mg and its comparators (placebo and IFN ß-1a, respectively) (**Table 1**)
  - However, a higher percentage of patients in the MS trials had a baseline total bilirubin >1 x ULN compared with patients in the UC trial

Table 1. Patient demographics and clinical characteristics

Characteristic	UC (True North) Induction period Placebo (n=216)	UC (True North) Induction period Ozanimod 0.92 mg (n=796)	MS (SUNBEAM/RADIANCE) IFN ß-1a 30 µg (n=885)	MS (SUNBEAM/RADIANCE) Ozanimod 0.92 mg (n=882)
Age, y, mean (SD)	41.9 (13.6)	41.7 (13.6)	35.6 (9.1)	35.4 (9.1)
Sex, n (%)				
Male	143 (66.2)	459 (57.7)	283 (32.0)	306 (34.7)
Female	73 (33.8)	337 (42.3)	602 (68.0)	576 (65.3)
Race, n (%)				
White	192 (88.9)	706 (88.7)	875 (98.9)	876 (99.3)
Asian	17 (7.9)	48 (6.0)	1 (0.1)	1 (0.1)
Black or African American	4 (1.9)	24 (3.0)	7 (0.8)	5 (0.6)
Other	3 (1.4)	18 (2.3)	2 (0.2)	0
Region, n (%)				
Eastern Europe	112 (51.9)[a]	415 (52.1)[a]	795 (89.8)	790 (89.6)
Western Europe	21 (9.7)[b]	122 (15.3)[b]	NA	NA
North America	60 (27.8)	187 (23.5)	NA	NA
Other	23 (10.6)[c]	72 (9.0)[c]	NA	NA
Rest of the world	NA	NA	90 (10.2)[d]	92 (10.4)[d]
BMI, kg/m², mean (SD)	25.1 (4.5)	25.6 (5.6)[e]	24.2 (5.0)	24.3 (4.8)[f]
Time since diagnosis, y, mean (SD)	6.8 (7.0)	7.4 (7.0)	3.7 (4.5)	3.8 (4.7)
Time since symptom onset, y, mean (SD)	7.6 (7.1)	8.3 (7.5)	6.6 (6.0)	6.9 (6.3)
Extent of UC disease, n (%)				
Left-sided	134 (62.0)	505 (63.4)	NA	NA
Extensive	82 (38.0)	291 (36.6)	NA	NA
Total Mayo score,[g] mean (SD)	8.9 (1.4)	9.0 (1.5)	NA	NA
ALT >1 x ULN, n (%)	9 (4.2)	47 (5.9)	55 (6.2)	62 (7.0)
AST >1 x ULN, n (%)	6 (2.8)	24 (3.0)	12 (1.4)	25 (2.8)
Total bilirubin >1 x ULN, n (%)	1 (0.5)	5 (0.6)	44 (5.0)	35 (4.0)

[a]Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Greece, Hungary, Latvia, Moldova, Poland, Romania, Russia, Serbia, Slovakia, and Ukraine. [b]Austria, Belgium, Germany, Italy, Netherlands, and United Kingdom. [c]Asia, South Africa, and South America. [d]Belgium, Canada, Germany, Greece, Italy, New Zealand, Portugal, South Africa, Spain, Sweden, United Kingdom, and United States. [e]n=794. [f]n=881. [g]Sum of the baseline rectal bleeding, stool frequency, Physician's Global Assessment, and endoscopy subscores.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IFN, interferon; MS, multiple sclerosis; NA, not applicable; SD, standard deviation; UC, ulcerative colitis; ULN, upper limit of normal.

LFTs

- The percentages of patients in the ozanimod 0.92 mg and comparator groups with elevations in ALT, AST, and bilirubin are shown in **Table 2**

Hy's law criteria and DILI

- UC trial: There were no Hy's law cases in either treatment group
- MS trials: The hepatic advisory board reviewed all cases of concurrent ALT and AST elevations ≥3 × ULN and bilirubin >2 × ULN (ie, there were 3 cases in the ozanimod 0.92 mg group and none in the IFN ß-1a group) and concluded that no cases met Hy's law criteria

Table 2. Maximum postbaseline elevations in ALT, AST, and bilirubin

Parameter	UC (True North) Placebo (n=216)	UC (True North) Ozanimod 0.92 mg (n=796)	MS (SUNBEAM/RADIANCE) IFN ß-1a 30 µg (n=885)	MS (SUNBEAM/RADIANCE) Ozanimod 0.92 mg (n=882)
Patients with an assessment, n	211	783	879	878
ALT				
>1 x ULN	21 (10.0)	215 (27.5)	244 (27.8)	373 (42.5)
≥3 x ULN	1 (0.5)	22 (2.8)	27 (3.1)	48 (5.5)
≥5 x ULN	1 (0.5)	8 (1.0)	11 (1.3)	14 (1.6)
≥10 x ULN	0	2 (0.3)	4 (0.5)	4 (0.5)
AST				
>1 x ULN	16 (7.6)	136 (17.4)	129 (14.7)	185 (21.1)
≥3 x ULN	0	14 (1.8)	19 (2.2)	9 (1.0)
≥5 x ULN	0	5 (0.6)	10 (1.1)	5 (0.6)
≥10 x ULN	0	0	2 (0.2)	4 (0.5)
Bilirubin				
>1 x ULN	10 (4.7)	32 (4.1)	102 (11.6)	122 (13.9)
>2 x ULN	1 (0.5)	3 (0.4)	2 (0.2)	14 (1.6)
>3 x ULN	0	1 (0.1)	0	3 (0.3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IFN, interferon; MS, multiple sclerosis; UC, ulcerative colitis; ULN, upper limit of normal.

Recovery and resolution of hepatic enzyme elevations

UC (True North)

- Of ozanimod-treated patients with ALT elevations ≥3 x ULN, 19/22 (86.4%) recovered to <3 x ULN within 3 months; most recovered while continuing treatment
- Of patients with AST elevations ≥3 x ULN, 12/14 (85.7%) ozanimod-treated patients recovered to <3 x ULN within 3 months; most recovered while continuing treatment
- Of patients with bilirubin elevations ≥2 x ULN, 2/3 (66.7%) ozanimod-treated patients recovered to <2 x ULN in 0.7 months while continuing treatment

MS (SUNBEAM/RADIANCE)

- Of patients with ALT elevations ≥3 x ULN, 41/48 (85.4%) receiving ozanimod 0.92 mg recovered to <3 x ULN within 3 months; most recovered while continuing treatment
- Of patients with AST elevations ≥3 x ULN, 5/5 (100%) patients receiving ozanimod 0.92 mg recovered to <3 x ULN while continuing treatment
- All bilirubin elevations >2 x ULN recovered to <2 x ULN while patients continued treatment

Hepatic TEAEs

- In the UC and MS trials, the incidences of symptomatic hepatic TEAEs across treatment groups were generally similar (**Table 3**)
  - Most TEAEs were mild to moderate in intensity
- Hepatic-related TEAEs (ie, generally asymptomatic laboratory abnormalities) leading to discontinuation were reported in 4 (0.5%) patients with UC and 11 (1.2%) patients with MS receiving ozanimod 0.92 mg (**Table 4**)
- No serious hepatic TEAEs occurred in either treatment group in the UC trial; in the MS trials, there were none in the ozanimod 0.92 mg group, but 3 occurred with IFN ß-1a (ie, cholelithiasis, chronic cholecystitis, and increased hepatic enzymes)
- No Hy's law cases or severe drug-induced hepatocellular injury occurred in patients receiving ozanimod in the UC and MS trials

Conclusions

- In this analysis of phase 3 UC and MS trials with ozanimod, elevations of AST, ALT, and bilirubin were transient, were usually asymptomatic, and generally resolved without study drug discontinuation
- In the UC and MS trials, the incidences of hepatic TEAEs were similar between treatment groups, and therapy discontinuations due to hepatic TEAEs were low
- No serious hepatic TEAEs occurred with ozanimod 0.92 mg in the UC and MS trials
- No Hy's law cases or severe DILI occurred with ozanimod 0.92 mg in the UC and MS trials

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