Design of a Study to Evaluate the Safety of Administering Ocrelizumab per a Shorter Infusion Protocol in Patients With Primary Progressive Multiple Sclerosis and Relapsing Multiple Sclerosis

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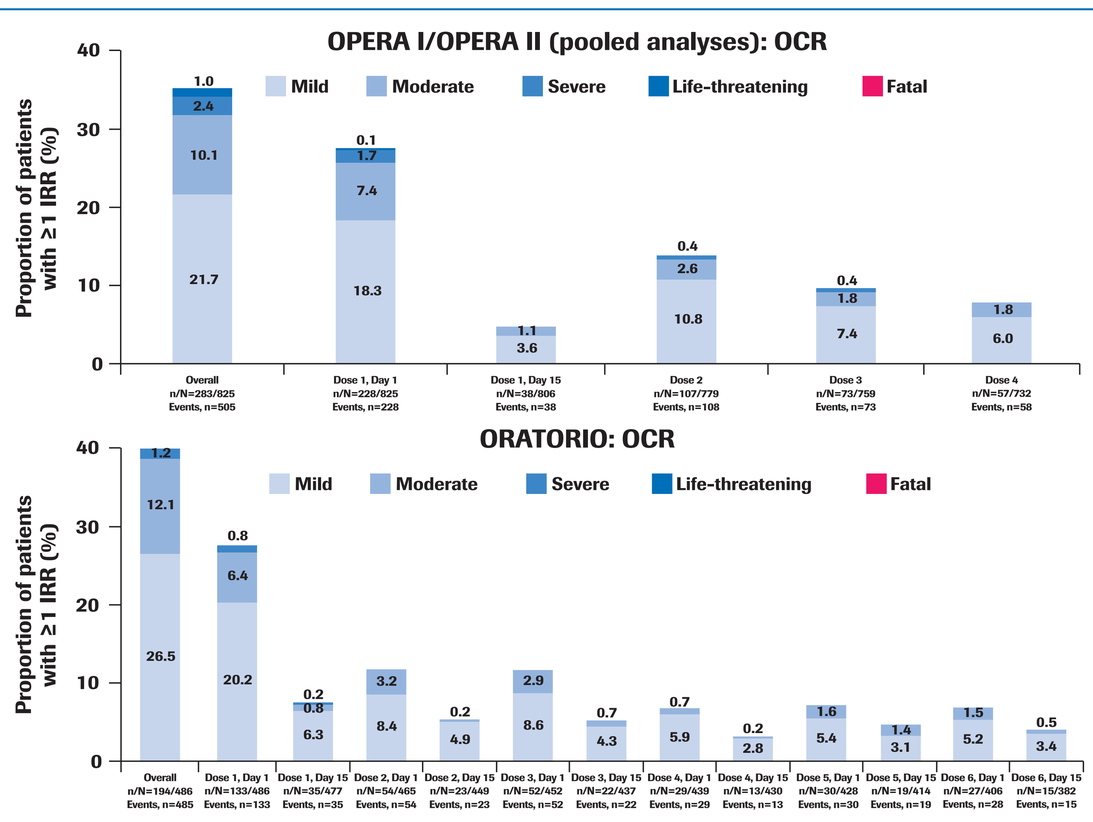
INTRODUCTION

- Ocrelizumab (OCR) is a humanised monoclonal antibody that selectively targets CD20-expressing B cells and has been approved for treatment of relapsing and primary progressive forms of multiple sclerosis (RMS and PPMS, respectively)[1,2]
- OCR is administered via intravenous infusion
  - In the OPERA and ORATORIO trials,[3,4] all patients received the first dose as 2 x 300 mg infusions 14 days apart. Patients in the ORATORIO[4] trial continued to receive divided dosing every 24 weeks whereas OPERA[3] patients received subsequent doses as single 600-mg infusions every 24 weeks
  - Per the US and EU prescribing information,[1,2] all patients follow the OPERA[3] dosing schedule

Infusion-Related Reactions (IRRs) in OCR Pivotal Studies

- In pivotal trials of OCR in patients with RMS (OPERA I [NCT01247324], OPERA II [NCT01412333])[3] and PPMS (ORATORIO [NCT01194570]),[4] IRRs were among the most common adverse events (AEs), similar to findings from clinical trials of other monoclonal antibody treatments[5–8]
  - IRRs were defined as any event that occurred during infusion or within 24 hours after infusion[9]
  - IRRs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0[10] as mild (Grade 1: asymptomatic or mild symptoms), moderate (Grade 2: moderate; minimal, local or noninvasive intervention indicated), severe (Grade 3: severe or medically significant), life-threatening (Grade 4: life-threatening consequences, urgent intervention indicated) or death related to AE (Grade 5)[9]
  - Serious IRRs were defined as events that were fatal or life-threatening, required hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability or incapacity or were otherwise considered medically significant or required intervention to prevent one of the previously listed outcomes
  - In general, IRRs in OCR-treated patients who were enrolled in the pooled OPERA and ORATORIO studies were mostly mild to moderate and decreased in severity with repeated infusions (**Figure 1**)[9,11]
    - The most frequent IRRs occurring in ≥5% of OCR-treated patients in the pooled OPERA and ORATORIO studies were pruritus, rash, throat irritation, flushing, pyrexia and headache[9]
    - Serious IRRs were reported in one OCR-treated patient from the pooled OPERA studies (Grade 4 bronchospasm) in association with the initial OCR infusion and five OCR-treated patients in ORATORIO (tachycardia, pyrexia, chills, nausea, vomiting, pruritis, hypertension and hypotension at the first infusion [n=2]; fever, asthenia and psychomotor retardation at Dose 2, Day 1 [n=1]; muscle spasticity at Dose 5, Day 15 [n=1]; and prolonged QT interval and hypotension at Dose 8, Day 15 [n=1])[9]

Figure 1. Percentage of patients with IRRs by dose and severity in the pooled OPERA and ORATORIO trials[11]



IRR, infusion-related reaction; OCR, ocrelizumab.

- To minimize the occurrence of IRRs, pre-infusion prophylaxis was required for all participants of the pivotal trials,[3,4] including a mandatory infusion of methylprednisolone 100 mg (or equivalent) 30 minutes before initiating each OCR infusion; optional prophylaxis with analgesics, antipyretics and/or antihistamines was also recommended 30 to 60 minutes before OCR infusion[9]
  - Per US[1] and EU[2] label recommendations, patients are required to receive premedication with both methylprednisolone (30 minutes before) and an antihistamine (30–60 minutes before), with a recommendation for additional analgesic treatment
  - Patients are also monitored in the clinic for ≥1 hour after infusion[1,2]

Optimizing the Infusion Duration of OCR Treatment

- Aside from the potential for IRRs, another important consideration with infusion therapies is duration of the infusion, since shortening the infusion can have a beneficial impact on patient satisfaction[12] while saving significant time;[13,14] furthermore, shorter infusions can have a positive impact on healthcare resources by saving time and costs[12–14]
- When administered according to label recommendations,[1,2] OCR infusions take a minimum of 2.5 hours for the first dose to ≥3.5 hours for subsequent doses (**Table 1**)
- Considering the additional time required for setting up the infusion, completing the premedication protocol and in-clinic monitoring following infusion as well as any travel time required to get to/from the infusion centre, patients may be giving up 5 to 6 hours or more per infusion
- Here we describe the design of a study intended to evaluate the safety and tolerability of OCR infused over a shorter period than is currently recommended
  - A separate substudy, ENSEMBLE PLUS, is investigating the impact of reducing infusion time on OCR-related IRRs under a double-blind setting in a subgroup of eligible patients with early-stage relapsing-remitting MS from the ongoing Phase IIIb, open-label, single-arm ENSEMBLE trial (NCT03085810; please refer to poster 68 for further details)

Table 1. Recommended infusion rate schedule for OCR treatment per the US label[1]

Time, min	Infusion rate, mL/hour	
	Initial dose (two 300-mg infusions, separated by 14 days)	Subsequent doses (600 mg every 24 weeks)
0–30	30	40
30–60	60	80
60–90	90	120
90–120	120	160
120–150	150	200
>150	180	200
>180	—	200
TOTAL INFUSION TIME	**≥2.5 hours[a]**	**≥3.5 hours[a]**

[a]Infusion time may be longer if the infusion is interrupted or slowed.

METHODS

Eligibility Criteria

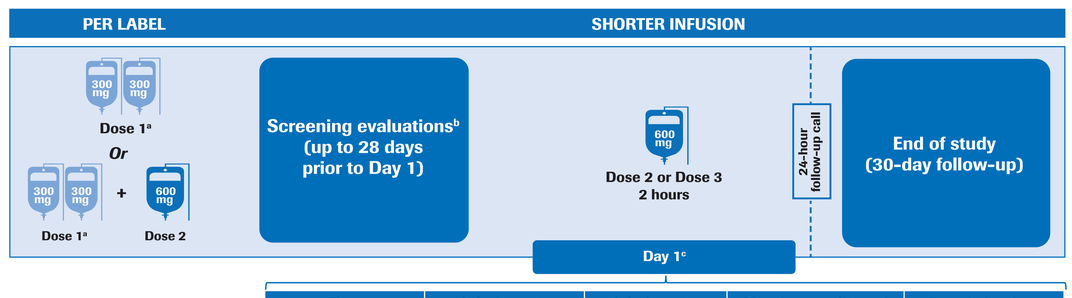
- This open-label, non-randomised study includes patients aged 18 to 55 years with RMS or PPMS (per 2017 McDonald criteria) and an Expanded Disability Status Scale score of 0 to 6.5; those who previously experienced a serious or life-threatening IRR with OCR are excluded

Treatment

- Patients are divided into two cohorts (**Figure 2**):
  - Patients in Cohort 1 complete OCR Dose 1 (300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion) or OCR Dose 1 and Dose 2 per the US prescribing information[1] prior to enrolment; these patients will receive their second or third dose of OCR 600 mg administered over a reduced infusion time of 2 hours (**Figure 2a**)
  - Patients in Cohort 2 receive the first 300-mg infusion of OCR Dose 1 over 2.5 hours per the US prescribing information[1] prior to enrolment; the second infusion of Dose 1 (300 mg) will be administered over a reduced time of 1.5 hours (**Figure 2b**)

Figure 2. Study design

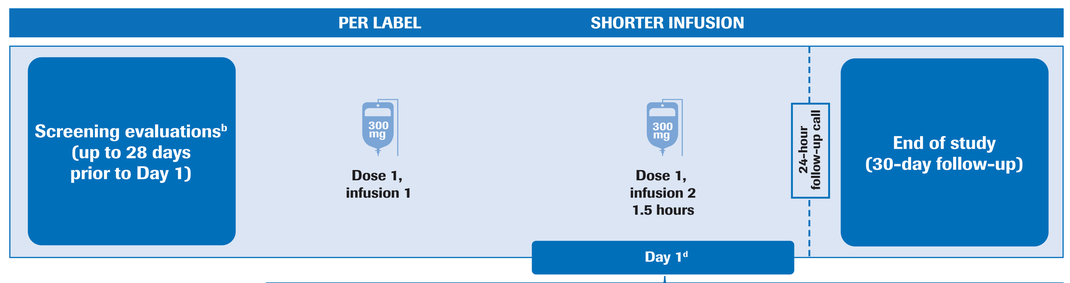
a. Cohort 1



Time (min)	Infusion rate (mL/hour)	Infusion rate (mg/hour)	Max dose per interval (mg)	Cumulative dose (mg)
0–15	100	120	30	30
15–30	200	240	60	90
30–60	250	300	150	240
60–90	300	360	180	420
90–120	300	360	180	600

Infusion time: 120 minutes. Preparation per US label: ocrelizumab 600 mg/normal saline 500 mL, toward a drug concentration of approximately 1.2 mg/mL.

b. Cohort 2



Time (min)	Infusion rate (mL/hour)	Infusion rate (mg/hour)	Max dose per interval (mg)	Cumulative dose (mg)
0–15	100	120	30	30
15–30	100	120	30	60
30–60	200	240	120	180
60–90	200	240	120	300

Infusion time: 90 minutes. Preparation per US label: ocrelizumab 300 mg/normal saline 250 mL, toward a drug concentration of approximately 1.2 mg/mL.

[a]Dose 1: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion per the US label[1]; [b]Certain protocol-defined tests are not part of standard-of-care laboratory evaluation panels. Patients must provide informed consent before these evaluations, obtained up to 6 months prior to the evaluations; patients' informed consent can also be obtained up to 6 months prior to study enrolment; [c]For Cohort 1, Dose 1 will be received prior to study enrolment per standard of care. Day 1 may occur at Week 24 or 48, depending on the previous treatment cycle; [d]For Cohort 2, Day 1 of infusion 1 is per standard of care.

Assessments

- A schedule of assessments is shown in **Table 2**
- The primary endpoint is the rate and frequency of NCI CTCAE Grade 3 and 4 IRRs in Cohort 1
- Secondary endpoints are the rate and frequency of Grade 3 and 4 IRRs in Cohort 2 and the rate and frequency of Grade 1 to 4 IRRs in both cohorts

Table 2. Schedule of assessments

	Screening (up to 28 days prior to Day 1)	Treatment visit	Phone follow-up (24 hours after infusion)	Safety follow-up visit (Day 30)
Informed consent[a]	X			
Medical history and demographics	X			
Review inclusion/exclusion criteria	X			
Physical examination	X			
Vital signs		X		
EDSS[b]	X			
Hematology	X			
Pregnancy test		X		
Adverse event assessment		X	X	X
Concomitant treatment review	X	X		X
Methylprednisolone and antihistamine premedication		X		
Ocrelizumab administration		X		

[a]Informed consent can be obtained up to 6 months prior to study enrolment; [b]EDSS assessment will not be performed if results are available within 6 months.
EDSS, Expanded Disability Status Scale.

RESULTS

- Enrolment began in the second half of 2018, with a planned enrolment of 100 patients in Cohort 1 and 50 patients in Cohort 2

CONCLUSIONS

- This study will provide information on the safety (i.e. Grade 3 and 4 IRRs) and tolerability of administering OCR per a shorter infusion protocol

DISCLOSURES

T Vollmer has received compensation for activities such as advisory boards, lectures and consultancy from the following companies and organizations: Academic CME, Alcimed, Anthem Blue Cross and Blue Shield, Roche/Genentech, Biogen IDEC, Novartis, Celgene, Epigene, Rocky Mountain Multiple Sclerosis Center, GLG Consulting, OhioHealth, TG Therapeutics, Topas Therapeutics, Dleara Lawyers and Teva Neuroscience. He has received research support from the following: Teva Neuroscience, NIH/NINDS, Rocky Mountain Multiple Sclerosis Center, Actelion, Biogen, Novartis, Roche/Genentech, UT Southwestern and TG Therapeutics, Inc.; E Alvarez has received personal compensation from Teva Neuroscience, Biogen, Genzyme, Genentech, Inc. and Novartis; and has received research support from Biogen, Teva and Novartis; KV Nair received compensation for activities such as advisory boards, lectures and consultancy from Biogen, Sanofi-Genzyme and Astellas and received institutional grants from Novartis, Genentech, Inc. and Biogen; J Cohen received personal compensation for consulting for Adamas, Alkermes, Convelo, EMD Serono, Gossamer Bio, Mapi, Novartis, and Pendopharm; speaking for Mylan and Synthon; and serving as a Co-Editor of Multiple Sclerosis Journal – Experimental, Translational and Clinical; A Boster has received consulting fees and/or fees for non-CME services from Biogen, Mallinckrodt, Medtronic, Novartis, Sanofi-Genzyme and Teva; D Masterman is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; A Pradhan is an employee of Genentech, Inc.; J Pei is an employee of Genentech, Inc., and a shareholder of F. Hoffman-La Roche Ltd; M Yang is an employee of Genentech, Inc., and a shareholder of F. Hoffman-La Roche Ltd; A Bobbala is an employee of Genentech, Inc.; B Moss has no conflict of interest to disclose.

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