Patient-Reported SymptoMScreen Baseline Scores in Patients With Relapsing-Remitting Multiple Sclerosis Enrolled In Phase IIIb Studies of Ocrelizumab (ENSEMBLE and CASTING)

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INTRODUCTION AND PURPOSE

- SymptoMScreen is a new patient-reported outcome (PRO) tool for the rapid assessment of multiple sclerosis (MS) symptom severity in routine clinical practice[1] and consists of 12 distinct domains assessed across a 7-point Likert scale ranging from 0 to 6 (**Figure 1**)
  - SymptoMScreen requires additional validation and is being used for the first time as a PRO measure in two ongoing, open-label, single-arm, Phase IIIb clinical trials of ocrelizumab (OCR):
  - ENSEMBLE (NCT03085810): patients are treatment naive with early-stage relapsing-remitting MS (RRMS)
  - CASTING (NCT02861014): patients have RRMS and a prior suboptimal response to disease-modifying treatment (DMT)
- The purpose of this presentation is to report baseline SymptoMScreen findings from the ENSEMBLE and CASTING studies

Figure 1. SymptoMScreen domains and Likert scale

Please circle **one number that best describes how MS has affected each function.** For example, if it takes you longer to type or text, you might rate your hand function as 'mildly limited' (circle '2'), but if you gave up typing completely, you might rate your hand function as 'very limited' (circle '4')

	0 – not affected at all	1 – very mild limitation / I make minor adjustments	2 –mild limitation / I make frequent adjustments	3 – moderate limitation / I reduced my daily activities	4 – severe limitation / I gave up some activities	5 – very severe limitation / I'm unable to do many daily activities	6 – total limitation / I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Aches, tenderness	0	1	2	3	4	5	6
Sensory symptoms Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress; panic attacks	0	1	2	3	4	5	6

MS, multiple sclerosis

METHODS

Study Design

- Patients in both ENSEMBLE and CASTING[1] received intravenous OCR 600 mg/24 weeks
  - The first OCR dose was administered as 2 × 300 mg doses administered 14 days apart
  - The treatment duration in ENSEMBLE is 192 weeks (maximum 8 doses) and in CASTING is 96 weeks (maximum 4 doses)
- SymptoMScreen domain scores at baseline were recorded in ENSEMBLE and CASTING
  - For the purpose of these studies, the original English version of SymptoMScreen was translated into 22 languages (Arabic, Bulgarian, Croatian, Czech, Danish, Dutch, Estonian, Finnish, French, German, Greek, Hungarian, Italian, Norwegian, Polish, Portuguese, Romanian, Slovak, Slovene, Spanish, Swedish, Turkish)
  - SymptoMScreen total scores (0–72) and individual domain scores will be assessed annually over the entire duration of the two studies
  - SymptoMScreen is freely available to the research community
    - http://biomedical-advances.org/neuro-20175-6/
- Details of the CASTING study design[2] and baseline characteristics[3] have been presented previously

Please scan here for ENSEMBLE and CASTING study designs

PLACEHOLDER CODE

ENSEMBLE INCLUSION CRITERIA

- Patients in ENSEMBLE were MS treatment naive and had early-stage RRMS defined per 2010 revised McDonald criteria
  - Age 18–55 years
  - Expanded Disability Status Scale (EDSS) score at screening, ≤3.5
  - Disease duration, ≤3 years
  - ≥1 clinically reported relapse or ≥1 sign of MRI activity within 12 months of enrolment

CASTING INCLUSION CRITERIA

- Patients in CASTING had a diagnosis of RRMS per 2010 revised McDonald criteria and had previously received ≤2 prior DMTs, with discontinuation of the most recent DMT due to suboptimal disease control within 12 months of enrolment
  - Suboptimal disease control is defined as having ≥1 clinically reported relapse(s) or ≥1 T1 gadolinium-enhancing lesion(s)/≥2 new/enlarging T2 lesions on MRI while being on a stable dose of the same DMT for ≥6 months
  - In patients receiving stable doses of the same approved DMT for >1 year, events must have occurred within the last 12 months of treatment with this DMT
- Additionally, patients are aged 18–55 years (inclusive), have an EDSS score ≤4.0 at screening and a disease duration <10 years

RESULTS

Baseline Characteristics

- A total of 678 patients were enrolled in ENSEMBLE and 680 patients were enrolled in CASTING
- Baseline characteristics of patients within ENSEMBLE (**Table 1a**) and CASTING (**Table 1b**) were reflective of treatment-naive patients with early-onset RRMS and patients with RRMS and a prior suboptimal response to DMTs, respectively
- CASTING prior MS DMT use:[2]
  - 60% of patients (n=412) had received one DMT and 40% of patients (n=269) received two DMTs prior to enrolment; the most frequently used DMT prior to enrolment was dimethyl fumarate (25%; n=168)

Table 1a. Baseline characteristics in ENSEMBLE

Parameter	ENSEMBLE (N=678) Treatment naive Early RRMS
Age, mean (SD), years	32.4 (9.1)
Female, n (%)	438 (65)
Caucasian, n (%)	563 (83)
BMI, mean (SD), kg/m²	25.6 (5.8)
Duration since MS symptom onset, mean (SD), years	1.1 (0.8)
Baseline EDSS score, mean (SD)	1.7 (1.0)
Number of relapses in last year, mean (SD)[a]	1.5 (0.9)
Enrolled due to, n (%):	
Only MS relapse	104 (15)[b]
Only MRI activity	72 (11)
Both relapse and MRI activity	502 (74)

Table 1b. Baseline characteristics in CASTING[2]

Parameter	CASTING (N=680) RRMS Suboptimal response to prior DMT
Age, mean (SD), years	34.2 (8.6)
Female, n (%)	436 (64)
Caucasian, n (%)	624 (92)
BMI, mean (SD), kg/m²	25.0 (5.4)
Duration since MS symptom onset, mean (SD), years	5.0 (2.7)
Baseline EDSS score, mean (SD)	2.1 (1.1)
Number of relapses in last year, mean (SD)[a]	1.2 (0.9)
Enrolled due to, n (%):	
Only MS relapse	238 (35)[b]
Only MRI activity	167 (25)
Both relapse and MRI activity	275 (40)

[a]Annualised relapse rate calculated in the year prior to enrolment; [b]Either ≥1 T1 gadolinium-enhancing lesion(s) or ≥2 new/enlarging T2 lesions.
BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Total, Individual Domain and Categorical Total SymptoMScreen Scores at Baseline

- Mean (CI) total scores and individual domain scores, and mean total categorical SymptoMScreen scores at baseline, are presented in **Figure 2** and **Figure 3**, respectively

Figure 2. Mean total and individual SymptoMScreen domain scores at baseline

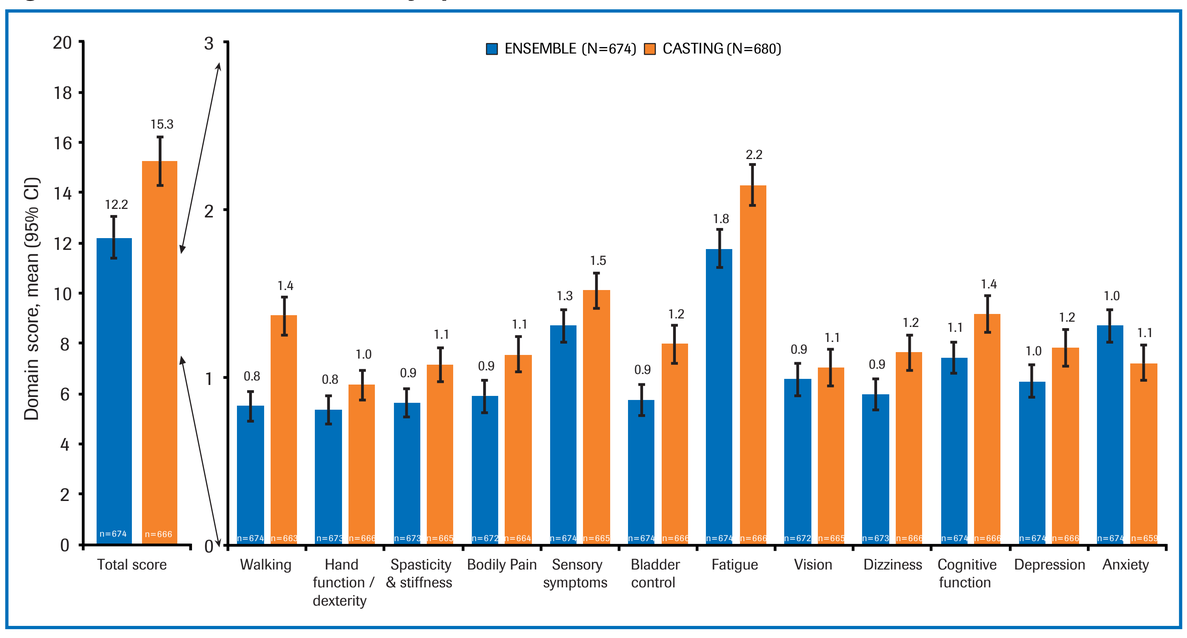
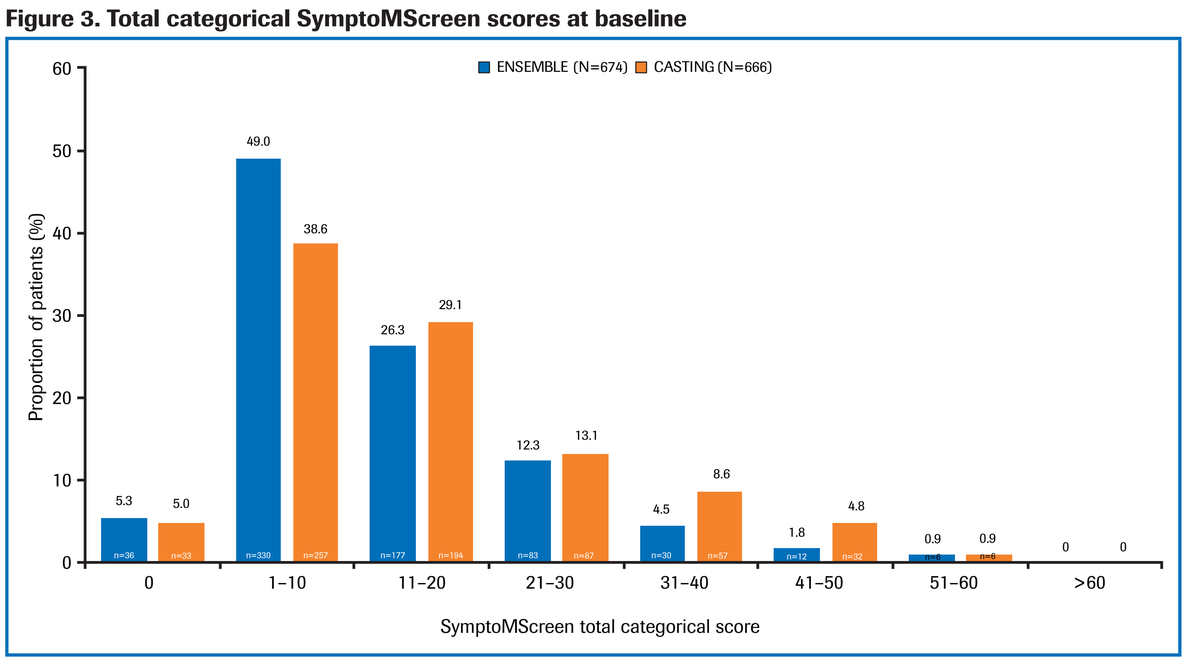


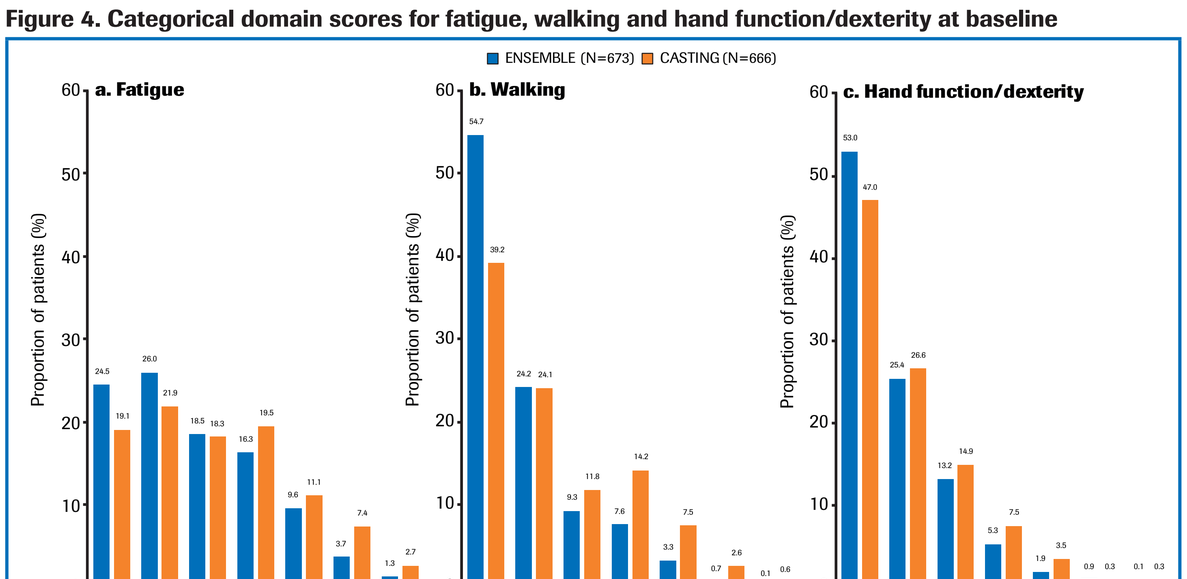
Figure 3. Total categorical SymptoMScreen scores at baseline



- Mean (CI) total SymptoMScreen scores at baseline were lower in ENSEMBLE than in CASTING
  - Median [range] total baseline SymptoMScreen scores were also lower at baseline in ENSEMBLE (9.0 [0.0–59.0]) than in CASTING (12.0 [0.0–57.0])
- In both ENSEMBLE and CASTING:
  - Fatigue was the domain with the highest score
  - Walking was the domain with the largest differential score between studies
  - Hand function/dexterity was the domain with the lowest domain score
  - Categorical domain scores for fatigue, walking and hand function/dexterity in ENSEMBLE and CASTING at baseline are presented in **Figure 4**

Categorical Domain Scores for Fatigue, Walking and Hand Function/Dexterity at Baseline

Figure 4. Categorical domain scores for fatigue, walking and hand function/dexterity at baseline



- Fatigue: moderate to severe impairment reported in 31% of patients in ENSEMBLE (n=209) and 41% of patients in CASTING (n=271)
- Walking: moderate to severe impairment reported in 12% of patients in ENSEMBLE (n=79) and 25% of patients in CASTING (n=165)
- Hand function/dexterity: moderate to severe impairment reported in 8% of patients in ENSEMBLE (n=56) and 12% of patients in CASTING (n=77)

CONCLUSIONS

- Baseline SymptoMScreen scores in patients in ENSEMBLE and CASTING were generally low
- Patient SymptoMScreen scores were higher at baseline in CASTING than ENSEMBLE, consistent with greater disability and longer disease duration in patients with suboptimal disease control under prior MS DMTs (CASTING) compared with a less disabled population early in their RRMS course (ENSEMBLE)
  - Differences in domain score between the two study populations were generally consistent
  - All domains contributed to the difference
  - Domain with the highest score in ENSEMBLE and CASTING: Fatigue
  - Domain with the lowest score in ENSEMBLE and CASTING: Hand function/dexterity
  - Domain with the highest differential score between ENSEMBLE and CASTING: Walking
- These data help to validate the use of SymptoMScreen as a patient-centric tool for the rapid assessment of MS symptoms

DISCLOSURES

G Cutter has served on data and safety monitoring boards for AMO Pharmaceuticals, BioLineRx, Horizon Pharmaceuticals, Merck, Merck/Pfizer, OPKO Biologics, Neurim, Orphazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva Pharmaceuticals, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee); and has served on consulting or advisory boards for Atara Biotherapeutics, Axon, Biogen, Biotherapeutics, argenx, BrainStorm Cell Therapeutics, Charleston Labs Inc, Click Therapeutics, Genzyme, Genentech, GW Pharma, Klein-Buendel Inc., MedImmune, MedDay, Novartis, Roche, SciFluor, Somahlution, Teva Pharmaceuticals, TG Therapeutics and UT Houston; G Cutter is employed by the University of Alabama at Birmingham and is president of Pythagoras, Inc., a private consulting company located in Birmingham, AL, USA. HP Hartung has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck Serono, Novartis, Octapharma, Opexa, Teva and Sanofi. P Vermersch has received financial grant/research support from Biogen, Celgene, F. Hoffmann-La Roche Ltd, Genzyme and Merck and has received consulting fees from Almirall, Biogen, F. Hoffmann-La Roche Ltd, Genzyme, Novartis and Servier. R Buffels is an employee of F. Hoffmann-La Roche Ltd. R Kuhelj is an employee of F. Hoffmann-La Roche Ltd. F McDougall is an employee and shareholder of F. Hoffmann-La Roche Ltd. W Wei is an employee and shareholder of F. Hoffmann-La Roche Ltd. I Kister served on scientific advisory boards for Biogen Idec and Genentech and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen Idec, Serono, Genzyme and Novartis.

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