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Fatigue and Other Patient-Reported Outcomes in Patients With RRMS Who Switched to Ocrelizumab: 4-Year Data From CASTING-LIBERTO

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CASTING (NCT02861014), LIBERTO (NCT03599245)

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G Comi has received consultancy fees from Roche, Bristol Myers Squibb, Janssen and Novartis; and performed contracted research for BMS.

G Cutter has served on the following data and safety monitoring boards: AI Therapeutics, AMO Pharma, AstraZeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Horizon Pharmaceuticals, Immunic, Mapi Pharmaceuticals Ltd, Merck, Mitsubishi Tanabe Pharma Holdings, Opko Biologics, Prothena Biosciences, Novartis, Regeneron, Sanofi-Aventis, Reata Pharmaceuticals, NHLBI (Protocol Review Committee), University of Texas Southwestern, University of Pennsylvania and Visioneering Technologies, Inc.; consulting or advisory boards: Alexion, Antisense Therapeutics, Biogen, Clinical Trial Solutions LLC, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein-Buendel, Inc., Merck-Serono, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Protalix Biotherapeutics, Recursion/Cerexis Pharmaceuticals, Regeneron, Roche and SAB Biotherapeutics; is employed by the University of Alabama at Birmingham and is President of Pythagoras, Inc., a private consulting company located in Birmingham, AL.

C Oreja-Guevara has received honoraria for speaking and serving on advisory boards from Biogen Idec., F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis and Teva.

S Clinch is an employee of and shareholder in F. Hoffmann-La Roche Ltd.

T Künzel is an employee of F. Hoffmann-La Roche Ltd.

P Dirks is an employee of F. Hoffmann-La Roche Ltd.

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Background

- PROs play an important role in the overall assessment of PwMS, providing valuable information about the impact MS has on patients' lives
- PwMS experience many different symptoms that affect their working capacity as well as physical and psychologic wellbeing
- Fatigue is one of the most common symptoms reported among PwMS
- OCR is a humanized monoclonal antibody that selectively targets $CD20^+$ B cells and reduces the rates of disease activity and progression in PwRRMS or PPMS[1,2]
- The 2-year, open-label, multicenter, Phase IIIb CASTING study examined the efficacy of OCR in PwRRMS who had a suboptimal response to ≥6 months of other DMTs
- Eligible patients were enrolled into the LIBERTO extension study for a further 2 years of follow-up

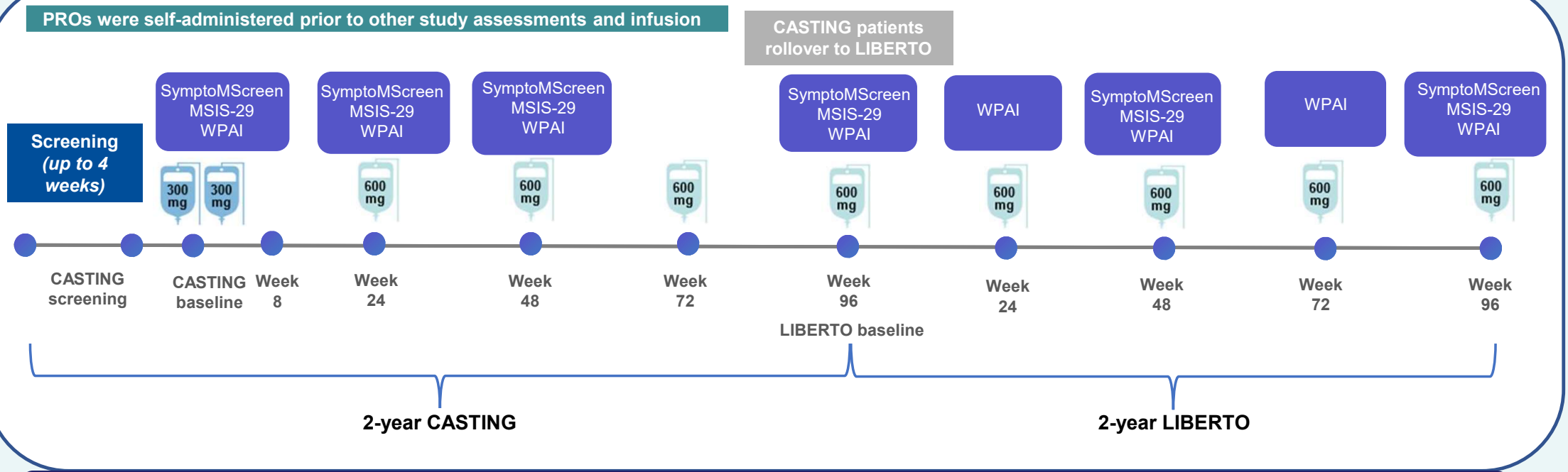
To report changes over 4 years of the CASTING-LIBERTO trial in PROs related to work productivity, physical and psychologic impact, and symptom limitations in PwRRMS who switched to OCR after suboptimal response to previous DMTs

DMT, disease-modifying therapy; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive MS; PRO, patient-reported outcomes; PwMS, people with multiple sclerosis; PwRRMS, people with relapsing-remitting multiple sclerosis.

1. Hauser SL, *et al. N Engl J Med* 2017;376:221–234. 2. Montalban X, *et al. N Engl J Med* 2017;376:209–220.

Methods: CASTING-LIBERTO study design

CASTING (NCT02861014) is an open-label, single-arm, Phase IIIb clinical study, in which patients received IV OCR 600 mg every 24 weeks for 96 weeks and a further 96 weeks if they rolled over into the LIBERTO study (NCT03599245). PROs were administered at the following time points:



Individuals aged 18 to 55 years with RRMS with a suboptimal response to one or two prior DMTs, disease duration of <10 years and EDSS score of ≤4 were included in CASTING. Patients who completed CASTING were eligible to rollover into LIBERTO

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IV, intravenous; MSIS-29, 29-item Multiple Sclerosis Impact Scale; OCR, ocrelizumab; PRO, patient-reported outcome; RRMS, relapsing-remitting multiple sclerosis; WPAI, Work Productivity and Activity Impairment.

Methods: PROs and correlation studies

Work productivity, symptom impact and symptom limitations were assessed by the WPAI, MSIS-29 and the SymptoMScreen questionnaires, respectively

WPAI[1]

The WPAI questionnaire is a 6-item PRO used to assess:

- Work time missed (absenteeism)
- Impairment while working (presenteeism)
- Overall work impairment (work productivity)
- Activity impairment

- Items are scored from free text (work hours missed) and on an 11-point scale ranging from 0 (had no effect on my work/daily activities) to 10 (problem completely prevented me from doing my work/daily activities)
- The patient is asked about the effect of their problem on their ability to work and perform regular activities, in the preceding 7 days
- Higher scores (each calculated as a percentage) indicate greater impact of MS on work and activities

MSIS-29[2]

The MSIS-29 is a 29-item PRO assessing physical and psychologic impacts of MS:

- "How much has your MS limited your ability to…"
- "How much have you been bothered by…"

- Each item is scored on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely)
- The Physical score (sum of items 1–20) is transformed onto a 0–100 scale
- The Psychological score (sum of items 21–29) is transformed onto a 0–100 scale
- 14-day recall period
- Higher scores indicate a greater impact of MS

SymptoMScreen[3,4]

The SymptoMScreen is a PRO used to assess the symptom limitations caused by 11 distinct domains commonly affecting PwMS

- Each domain is scored on a 7-point Likert scale ranging from 0 (unaffected) to 6 (total limitation)
- Domain scores are summed to calculate a total ranging from 0 to 72
- No defined recall period
- Higher scores indicate greater symptom limitations

Change in PROs was assessed.
Spearman's correlations were performed to determine if there was a relationship between fatigue and patients' work productivity or physical and psychologic impact

MS, multiple sclerosis; MSIS-29, 29-item Multiple Sclerosis Impact Scale; PRO, patient-reported outcome; PwMS, people with multiple sclerosis; WPAI, Work Productivity and Activity Impairment.

1. Reilly Associates. WPAI: SHP V2.0. August 2010. Available from: http://www.reillyassociates.net/WPAI_SHP.html. Accessed March 6, 2023. 2. Hobart H, *et al. Brain* 2001;124(5):962–973. Link to MSIS-29: https://mstrust.org.uk/sites/default/files/MSIS-29.pdf. 3. SymptoMScreen. 2018. Available from: https://www.symptomscreen.org/. Accessed March 6, 2023. 4. Green R, *et al. Appl Neuropsychol Adult* 2017;24(2):183–189.

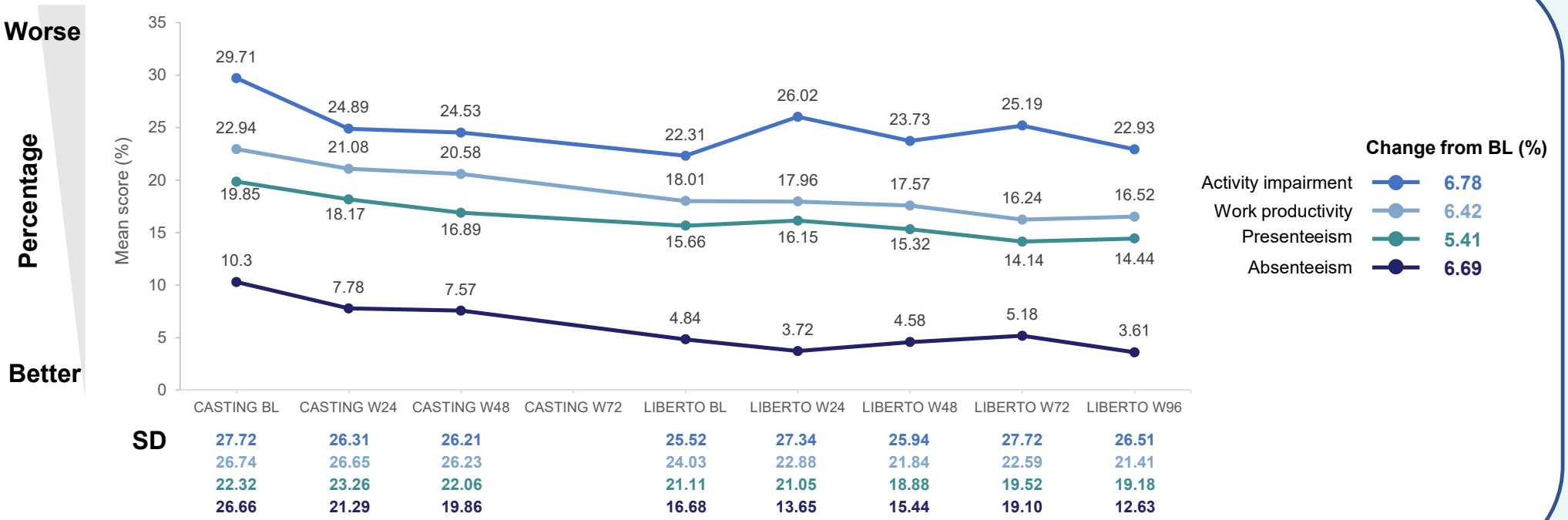
Results: Patient demographics and baseline characteristics

Parameter	CASTING total population (N=680)	LIBERTO population at CASTING BL (N=439)	Patient population that did not rollover into LIBERTO (N=241)
Mean age (SD), years	**34.2 (8.6)**	**34.0 (8.5)**	**34.4 (8.7)**
Age group, 40-year threshold, n (%)			
<40	486 (71.5)	318 (72.4)	168 (69.7)
≥40	194 (28.5)	121 (27.6)	73 (30.3)
Female, n (%)	**436 (64.1)**	**276 (62.9)**	**160 (66.4)**
Caucasian, n (%)[a]	**625 (91.9)**	**408 (92.9)**	**217 (90.0)**
Baseline EDSS, mean (SD)[b]	**2.09 (1.06)**	**2.03 (1.08)**	**2.21 (1.03)**

Baseline characteristics and demographics of patients who rolled over to LIBERTO were representative of the total CASTING population

[a]Patient is counted in more than one race when multiple races are checked; [b]Screening EDSS if baseline EDSS is not available.
BL, baseline; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Results: WPAI scores over 4 years from baseline

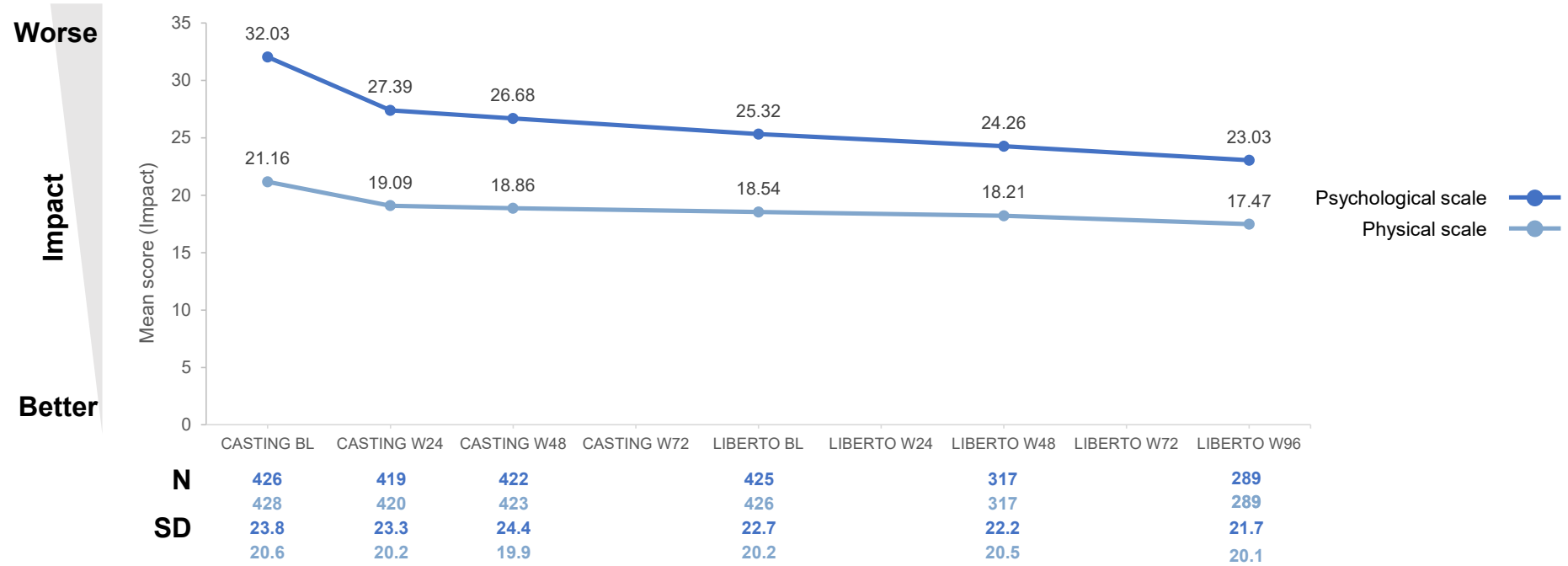


SD								
	27.72	26.31	26.21	25.52	27.34	25.94	27.72	26.51
	26.74	26.65	26.23	24.03	22.88	21.84	22.59	21.41
	22.32	23.26	22.06	21.11	21.05	18.88	19.52	19.18
	26.66	21.29	19.86	16.68	13.65	15.44	19.10	12.63

WPAI scores decreased over the 4-year study period

BL, baseline; SD, standard deviation; W, week; WPAI, Work Productivity and Activity Impairment.

Results: MSIS-29 Physical and Psychological scales over 4 years from baseline

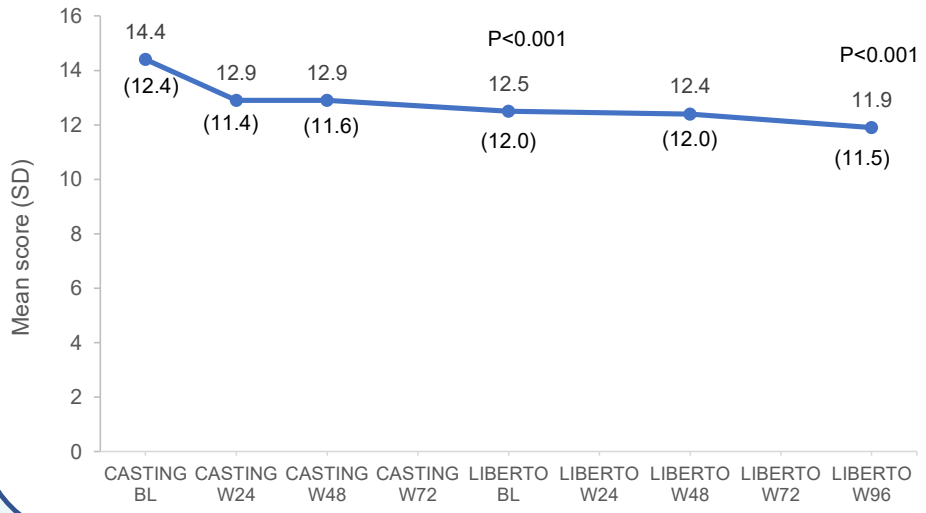


Patients experienced a decrease in physical and psychologic impacts of their MS over the 4-year study period. The largest decrease was observed during the first 24 weeks

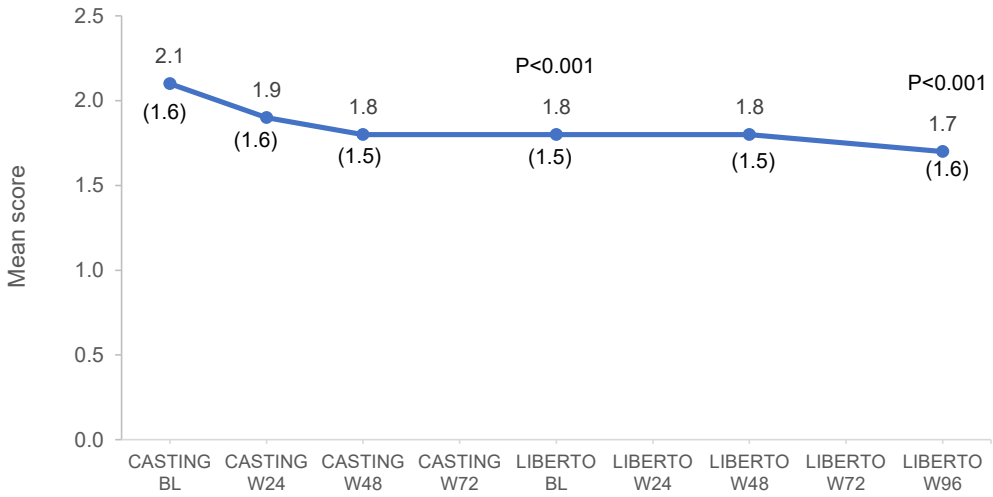
BL, baseline; MS, multiple sclerosis; MSIS-29, 29-item Multiple Sclerosis Impact Scale; SD, standard deviation; W, week.

Results: SymptoMScreen Total Score and Fatigue Score over 4 years from baseline[a,b]

SymptoMScreen mean Total score (SD) – from BL[a,b]



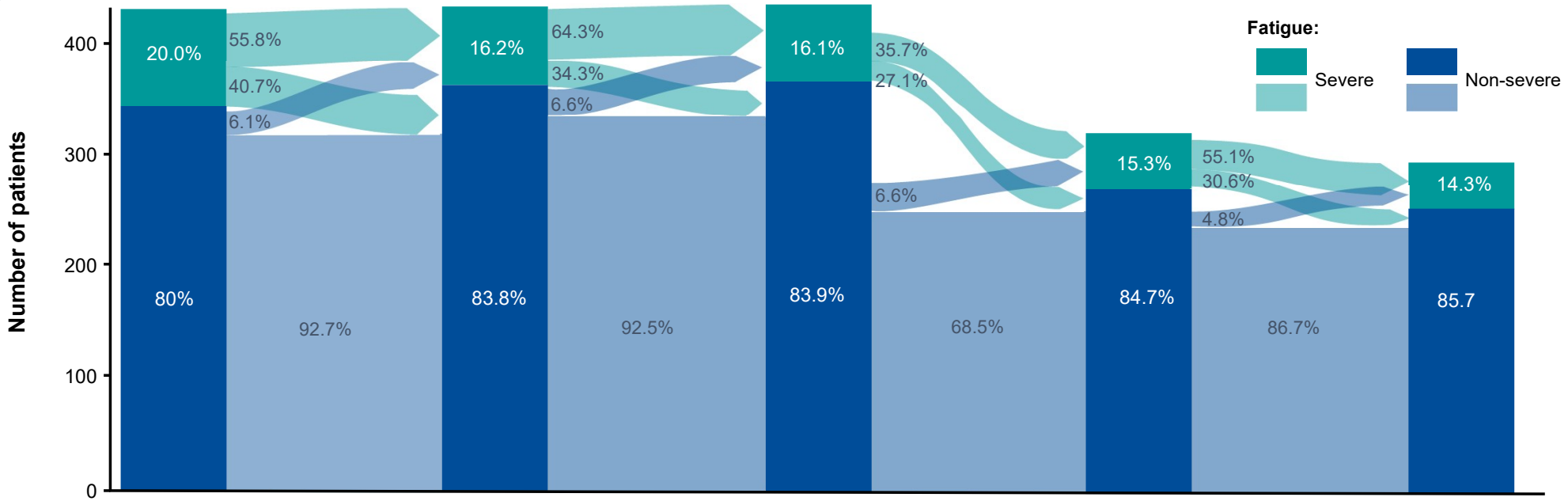
SymptoMScreen mean Fatigue score (SD) – from BL[a,c]



Mean SymptoMScreen domain scores were low at baseline, with an overall decrease over the 4-year study period. This trend was also observed for Fatigue, the domain with the highest SymptoMScreen scores at baseline. The largest decreases were observed during the first 24 weeks

[a]P-values reported are from CASTING BL to CASTING Week 96 and LIBERTO Week 96; [b]SymptoMScreen scored out of 72; [c]SymptoMScreen individual domains scored out of 7.
BL, baseline; SD, standard deviation; W, week.

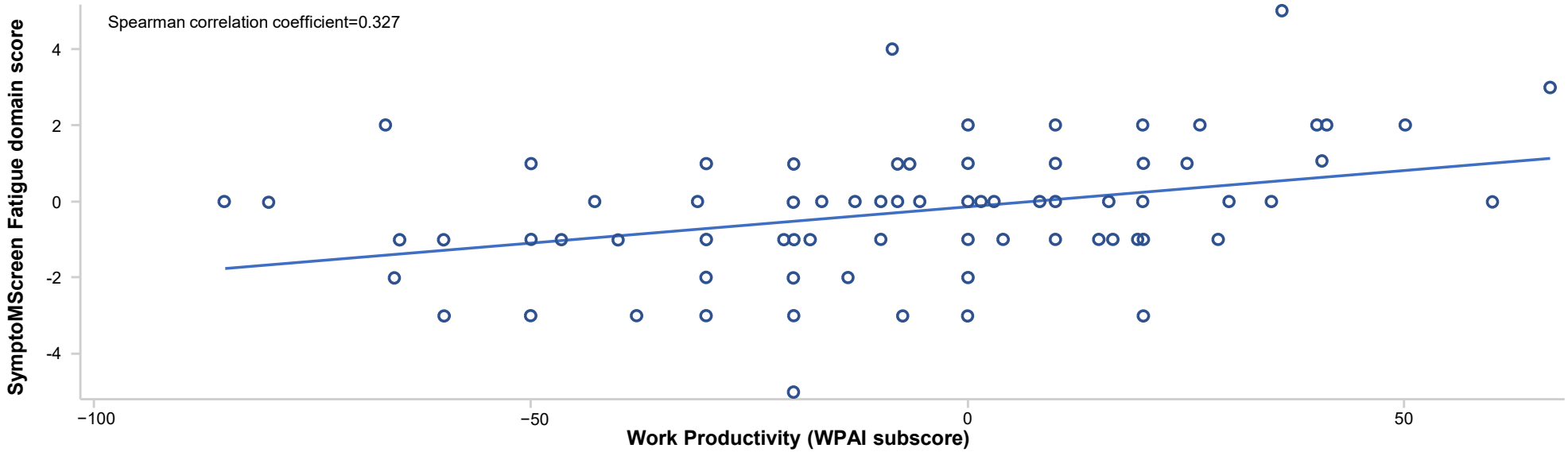
Results: Flow of SymptoMScreen Fatigue Score by Epoch from baseline[a]



Over the 4-year study period, fewer patients experienced fatigue as a severe symptom (SymptoMScreen score≥4) Sensory, cognition and walking were the other high scoring domains.[b]

[a]SymptoMScreen score ≥ 4 = severe limitation or worse; [b]See supplemental slides 17, 18 and 19.
BL, baseline; W, week.

Results: Correlation between change from SymptoMScreen Fatigue Score – change from baseline



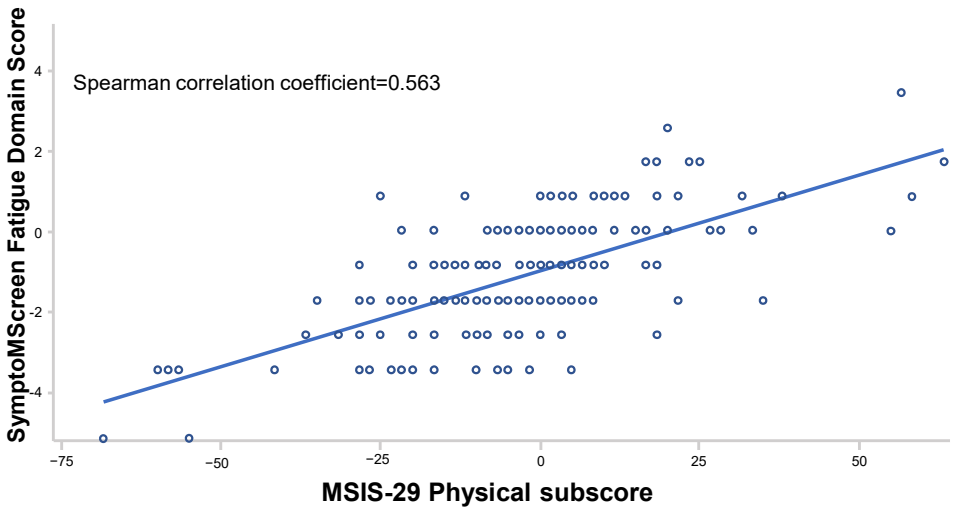
Changes in SymptoMScreen Fatigue item moderately correlated[1] with WPAI Work Productivity subscore, over the 4-year study period

WPAI, Work Productivity and Activity Impairment.

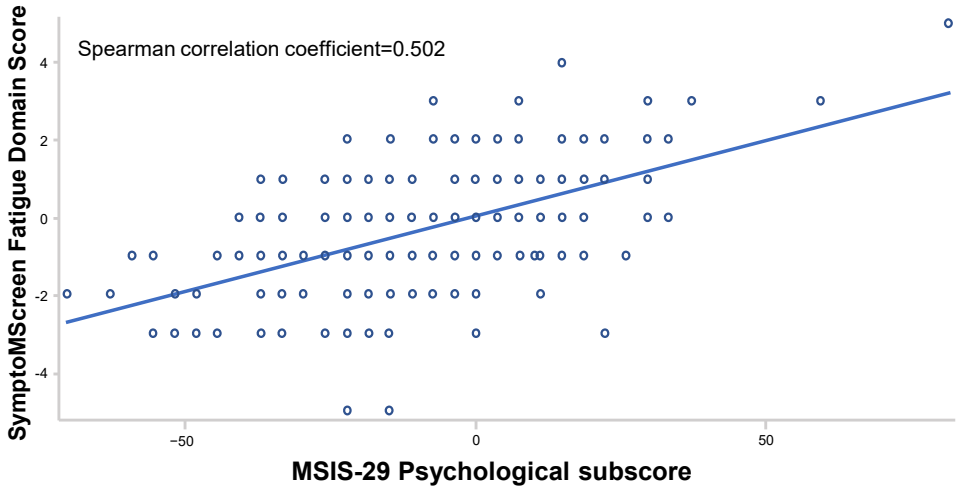
1. Cohen J. *Psych Bull*. 1992;112(1):155–9.

Results: Correlation between SymptoMScreen Fatigue Score and MSIS-29 (Physical and Psychological subscores)

Fatigue score and MSIS-29 (Physical subscore) – Change from BL



Fatigue score and MSIS-29 (Psychological subscore) – Change from BL



Change in SymptoMScreen Fatigue item strongly correlated[1] with change in MSIS-29 Physical and Psychological subscores, over the 4-year study period

BL, baseline; MSIS-29, 29-item Multiple Sclerosis Impact Scale.

1.Cohen J. *Psych Bull*. 1992;112(1):155–9.

Conclusions

- PwRRMS who switched to ocrelizumab due to suboptimal disease control on other DMTs reported low symptom impact at CASTING baseline, but maintained a numerical improvement over 4 years of ocrelizumab treatment in PROs used to assess:
  - Work productivity (WPAI)
  - Physical and psychologic impacts (MSIS-29)
  - Symptom limitations (SymptoMScreen)
- The Fatigue domain assessed within the SymptoMScreen was scored as the most limiting symptom at CASTING baseline and showed a sustained numerical improvement over 4 years
  - Improvement in the SymptoMScreen Fatigue domain moderately to strongly correlated with improvement in work productivity (WPAI) and improvement in MSIS-29 (Physical and Psychological subscores)

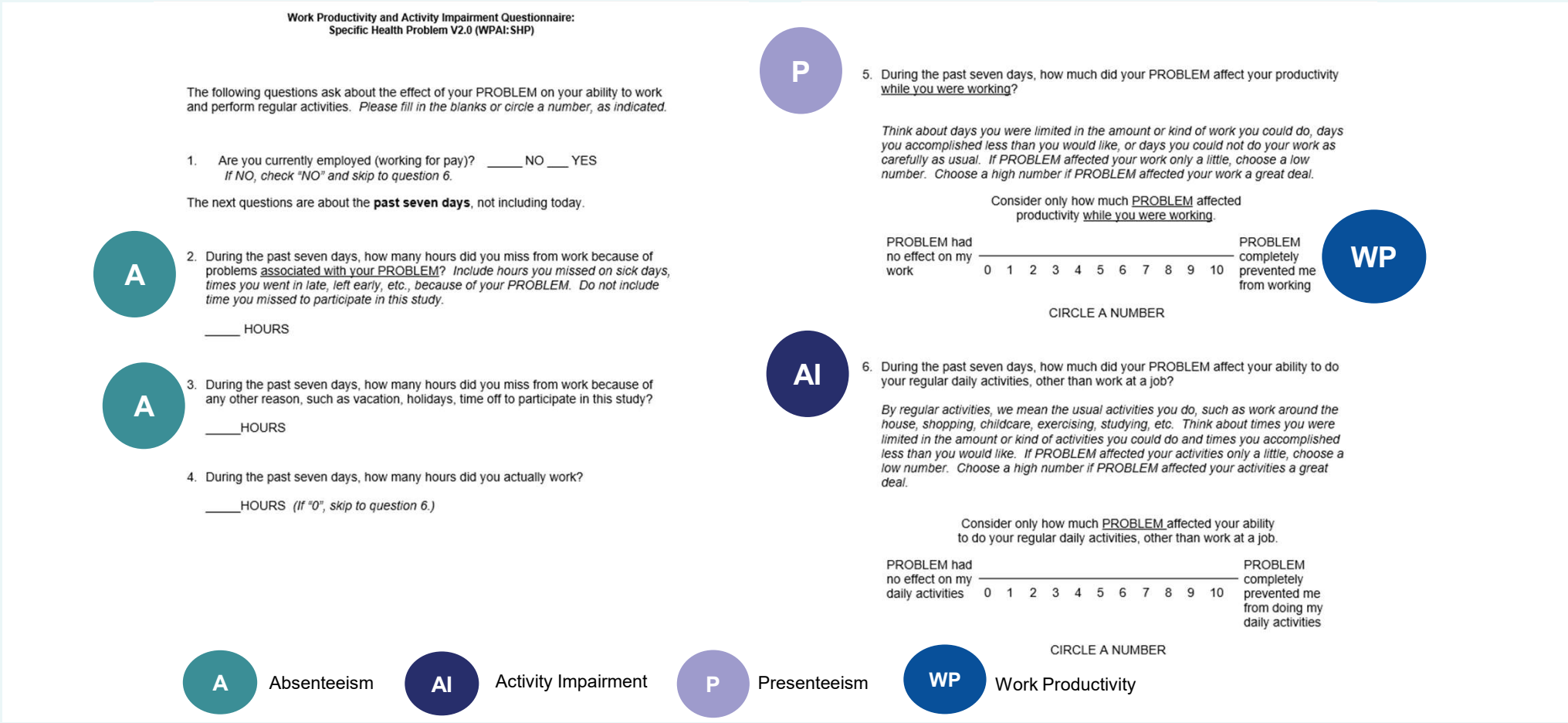
The 4-year CASTING-LIBERTO PRO data demonstrate the sustained treatment effect of ocrelizumab in patients who had a suboptimal response to prior DMTs

MSIS-29, 29-item Multiple Sclerosis Impact Scale; PRO, patient-reported outcome; PwRRMS, people with relapsing-remitting multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; WPAI, Work Productivity and Activity Impairment.

Acknowledgments: We would like to thank all patients, their families and the investigators who participated in this study

Supplemental Materials

Supplemental: WPAI[1]



Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your PROBLEM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

A

2. During the past seven days, how many hours did you miss from work because of problems associated with your PROBLEM? *Include hours you missed on sick days, times you went in late, left early, etc., because of your PROBLEM. Do not include time you missed to participate in this study.*

   _____ HOURS

A

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

P

5. During the past seven days, how much did your PROBLEM affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If PROBLEM affected your work only a little, choose a low number. Choose a high number if PROBLEM affected your work a great deal.

Consider only how much PROBLEM affected productivity while you were working.

PROBLEM had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — PROBLEM completely prevented me from working

WP

CIRCLE A NUMBER

AI

6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

Consider only how much PROBLEM affected your ability to do your regular daily activities, other than work at a job.

PROBLEM had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — PROBLEM completely prevented me from doing my daily activities

CIRCLE A NUMBER

A Absenteeism

AI Activity Impairment

P Presenteeism

WP Work Productivity

A, absenteeism; AI, activity impairment; P, presenteeism; WP, work productivity; WPAI, Work Productivity and Activity Impairment.

1. Reilly Associates. WPAI: SHP V2.0. August 2010. Available from: http://www.reillyassociates.net/WPAI_SHP.html. Accessed March 6, 2023.

Supplemental: SymptoMScreen[1]

SYMPTOMSCREEN

Please circle **one number that best describes how each MS symptom has affected your everyday life activities.** For example, if it takes you longer to type or text, your hand function may have a 'mild limitation' (circle '2'), but if you gave up typing or texting completely, your hand function may have a 'severe limitation' (circle '4').

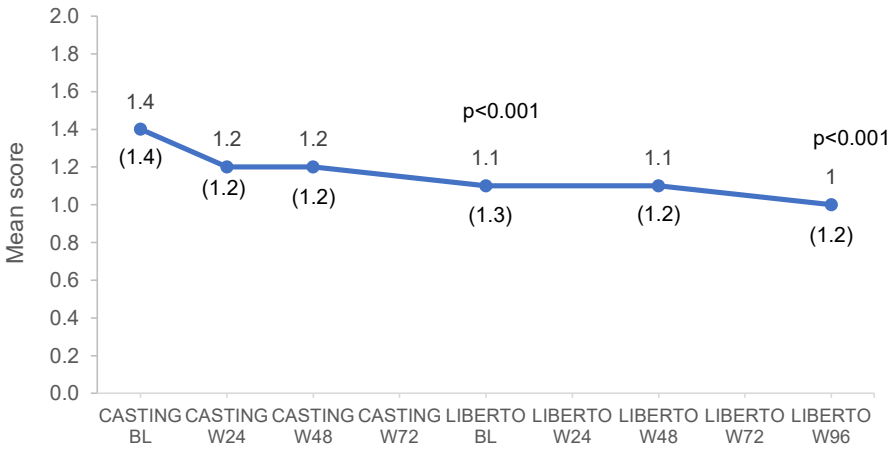
	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5 – very severe limitation/ I'm unable to do many daily activities	6 – total 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 Achiness, tenderness	0	1	2	3	4	5	6
Sensory Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, urinary 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.

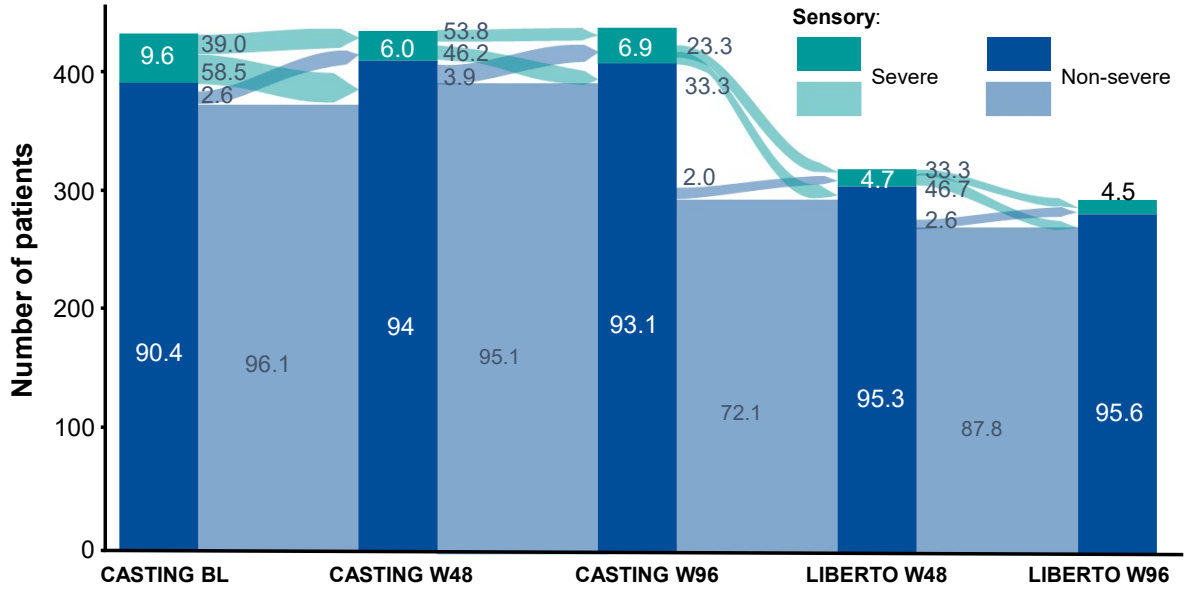
1. SymptoMScreen. 2018. Available from: https://www.symptomscreen.org/. Accessed March 6, 2023.

Results: SymptoMScreen Sensory Score over 4 years from baseline

SymptoMScreen mean Sensory score (SD) – from BL[a,b]



Percentage Flow of SymptoMScreen Sensory domain by Epoch – from BL[c,d]

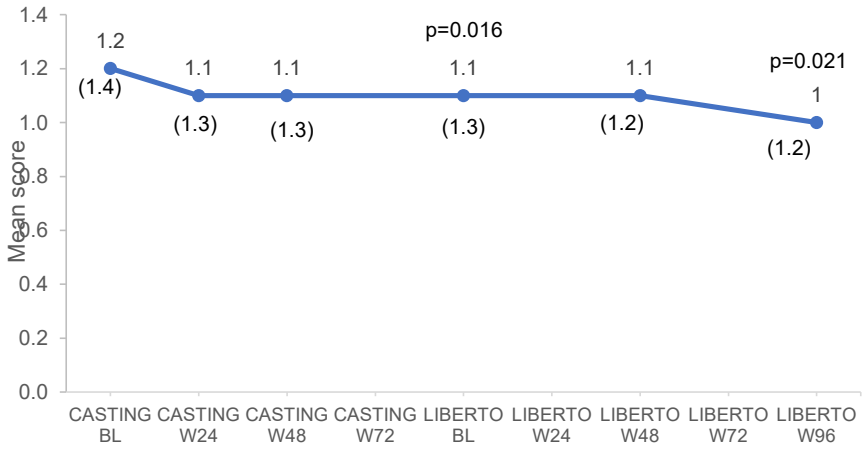


N	429	433	435	319	292
Severe	41	26	30	15	13
Non-severe	388	407	405	304	279

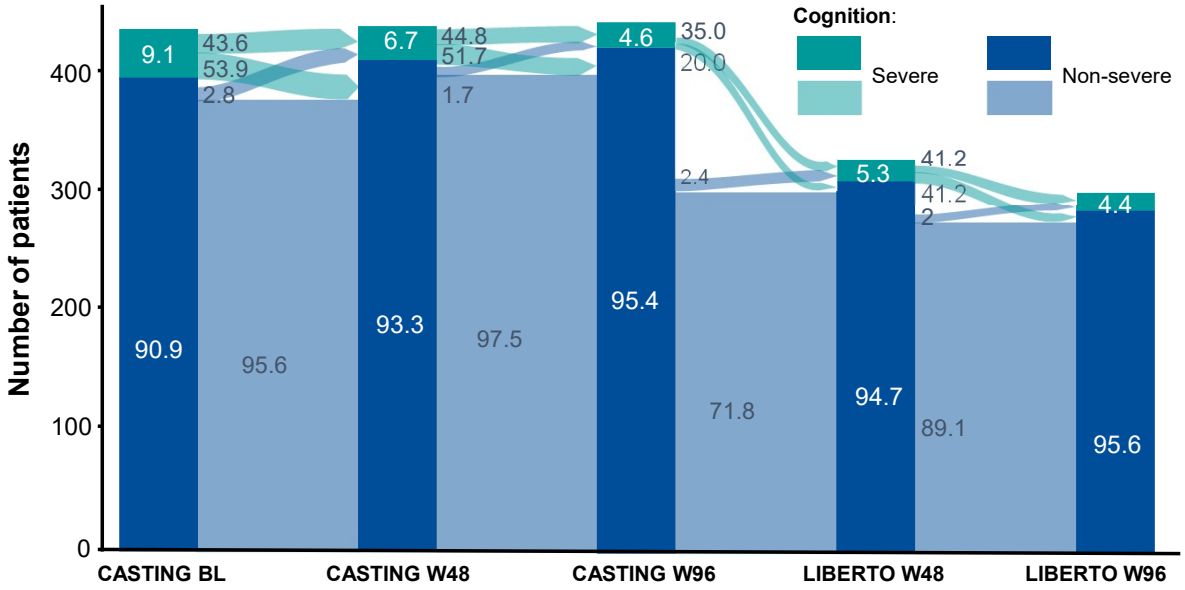
[a]P-values reported are from CASTING BL to CASTING Week 96 and LIBERTO Week 96; [b]SymptoMScreen individual domains scored out of 7; [c]SymptoMScreen score ≥ 4=severe limitation or worse;
[d]Percentage of patients with severe symptom limitations are reported under the bars.
BL, baseline; SD, standard deviation; W, week.

Results: SymptoMScreen Cognition Score over 4 years from baseline

SymptoMScreen mean Cognition score (SD) – from BL[a,b]



Percentage Flow of SymptoMScreen Cognition domain by Epoch – from BL[c,d]

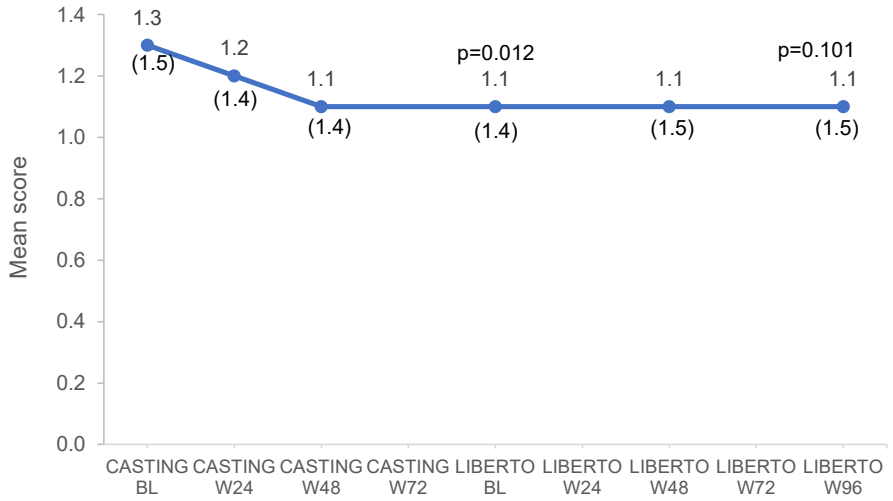


N	429	432	435	321	294
Severe	39	29	20	17	13
Non-severe	390	403	415	304	281

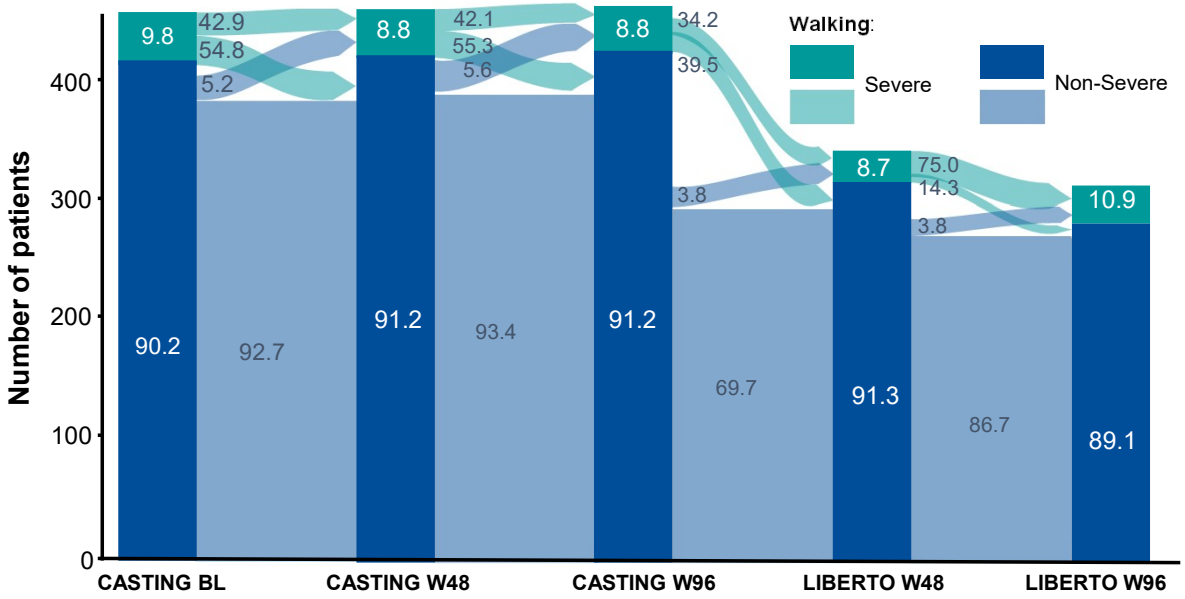
[a]P-values reported are from CASTING BL to CASTING Week 96 and LIBERTO Week 96; [b]SymptoMScreen individual domains scored out of 7; [c]SymptoMScreen score ≥ 4=severe limitation or worse;
[d]Percentage of patients with severe symptom limitations are reported under the bars.
BL, baseline; SD, standard deviation; W, week.

Results: SymptoMScreen Walking Score over 4 years from baseline

SymptoMScreen mean Walking score (SD) – from BL[a,b]



Percentage Flow of SymptoMScreen Walking domain by Epoch – from BL[c,d]



N	**427**	**430**	**434**	**321**	**293**
Severe	**42**	**38**	**38**	**28**	**32**
Non-severe	**385**	**392**	**396**	**293**	**261**

[a]P-values reported are from CASTING BL to CASTING Week 96 and LIBERTO Week 96; [b]SymptoMScreen individual domains scored out of 7; [c]SymptoMScreen score ≥ 4=severe limitation or worse;
[d]Percentage of patients with severe symptom limitations are reported under the bars.
BL, baseline; SD, standard deviation; W, week.