Efficacy of Daclizumab Beta vs Intramuscular Interferon Beta-1a on 24-Week Sustained Disability Progression Using a Modified Multiple Sclerosis Functional Composite

Cohan S,[1] Kappos L,[2] Giovannoni G,[3] Wiendl H,[4] Havrdova E,[5] Rose J,[6] Greenberg SJ,[7] Phillips G,[8] Riester K,[8] Lima G,[8] Sabatella G[8] *Presenter – Anna Maria Repice*

[1]Providence Multiple Sclerosis Center, Providence Brain and Spine Institute, Providence Health & Services, Portland, OR, USA; [2]Neurologic Clinic and Policlinic, Departments of Mediclinical Research and Biomedical Engineering, University Hospital, Basel, Switzerland; [3]Queen Mary University London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, UK; 4University of Münster, Münster, Germany; 5First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; 6Department of Neurology, University of Utah and Neurovirolgy Research Laboratory VASLCHCS, Imaging and Neuroscience Center, Salt Lake City, UT, USA; 7AbbVie Inc, North Chicago, IL, USA; 8Biogen, Cambridge, MA, USA

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INTRODUCTION

- Changes have been proposed to the Multiple Sclerosis Functional Composite (MSFC) to improve its use as an outcome measure.[1,2,3]
- One such change replaces the 3-second Paced Auditory Serial Addition Test (PASAT-3) with the Symbol Digit Modalities Test (SDMT), which is easier/faster for patients, does not depend on math ability and has smaller practice effects.[1,2]
- Analysing MSFC progression based on worsening of any MSFC component has been proposed by Rudick *et al*.[3]

OBJECTIVES

- Examine disability progression in DECIDE using a modified MSFC (MSFCS) comprising the Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT) and SDMT.

METHODS

- Patients received daclizumab beta (daclizumab)* 150 mg subcutaneous every 4 weeks or interferon (IFN) beta-1a 30 mcg intramuscular (IM) once weekly for ≥96 weeks (maximum 144 weeks).[4]
- Sustained MSFCS progression (defined as ≥20% worsening in T25FW, ≥20% worsening in 9HPT [mean of both hands][3] or ≥4-point decrease in SDMT,[5] sustained for 24 weeks) was examined post hoc in the intention-to-treat (ITT) population and in patient subgroups based on Baseline patient characteristics (Table).
- Additional analyses included examining MSFCS progression using a ≥20% worsening in the 9HPT for the dominant hand only, or for either the dominant hand or the non-dominant hand.

RESULTS

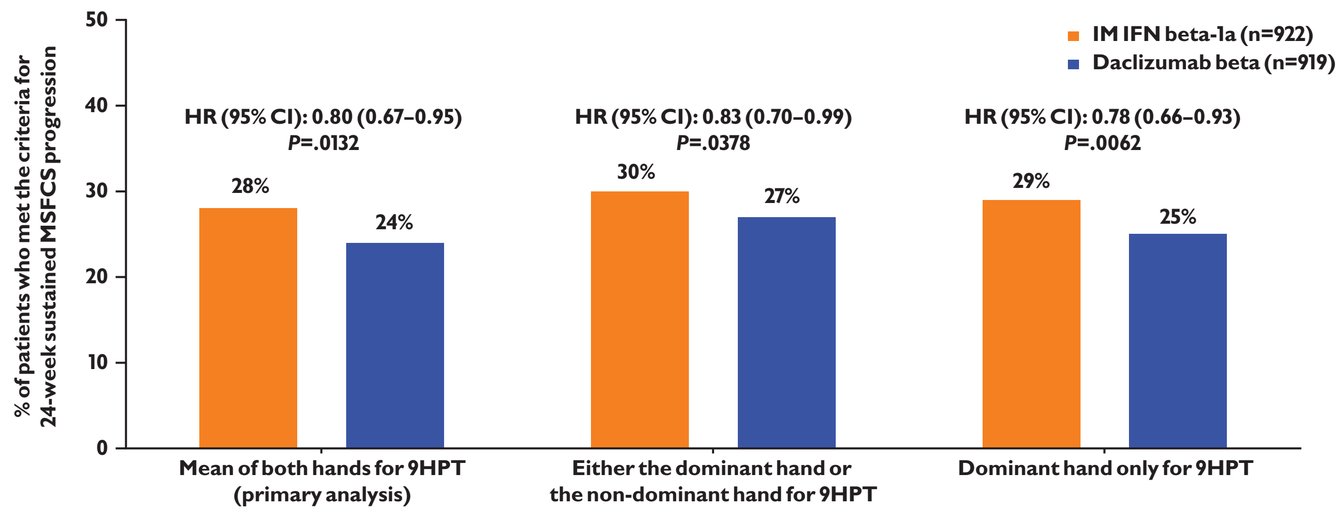
- Baseline demographic and clinical characteristics were similar between treatment groups (Table).
- In the overall population, 24% (224/919) of daclizumab beta patients and 28% (259/922) of IM IFN beta-1a patients met the criteria for 24-week sustained MSFCS progression (Figure 1).
- Of patients who progressed, MSFCS progression was driven most commonly by the SDMT (IM IFN beta-1a, 56% [146/259]; daclizumab beta, 55% [124/224]), followed by the T25FW (IM IFN beta-1a, 34% [89/259]; daclizumab beta, 33% [75/224]) and the 9HPT (IM IFN beta-1a, 6% [16/259]; daclizumab beta, 8% [17/224]). The rest of the patients progressed on ≥2 components at the same time.
- Daclizumab beta treatment resulted in a 20% relative reduction in risk of 24-week sustained MSFCS progression vs. IM IFN beta-1a (Figure 1) in the overall population.
- Similar results were observed for MSFCS progression using a ≥20% worsening of the 9HPT irrespective of the methodology employed for the 9HPT (Figure 1) and in subgroup analyses (data not shown).
- In subgroup analyses, point estimates showed consistent trends favouring daclizumab beta over IM IFN beta-1a across all subgroups investigated (Figure 2).

Table. Baseline demographics and disease characteristics

Characteristic	IM IFN beta-1a n=922	Daclizumab beta n=919
Mean (SD) age, y	36.2 (9.3)	36.4 (9.4)
White, n (%)	828 (90)	823 (90)
Mean (median) time since MS diagnosis, y	4.1 (2.0)	4.2 (2.0)
Mean (SD) no. of relapses in previous year	1.6 (0.8)	1.5 (0.7)
Mean (SD) no. of relapses in previous 3 years[a]	2.7 (1.3)	2.7 (1.2)
Baseline EDSS score		
Mean (SD)	2.5 (1.3)	2.5 (1.2)
Median (range)	2.2 (0–6.0)	2.0 (0–5.5)
Mean (SD) SDMT score[b]	**47.7 (16.1)**	**48.5 (15.9)**
Median (25th, 75th percentile) MSFC score[c]	**0.118 (–0.377, 0.482)**	**0.139 (–0.335, 0.491)**
MSFC components		
Median (25th, 75th percentile) T25FW z score	0.223 (–0.042, 0.372)	0.223 (–0.034, 0.372)
Median (25th, 75th percentile) 9HPT z score	0.035 (–0.622, 0.633)	0.065 (–0.597, 0.661)
Median (25th, 75th percentile) PASAT-3 z score[c]	0.264 (–0.619, 0.794)	0.352 (–0.531, 0.794)

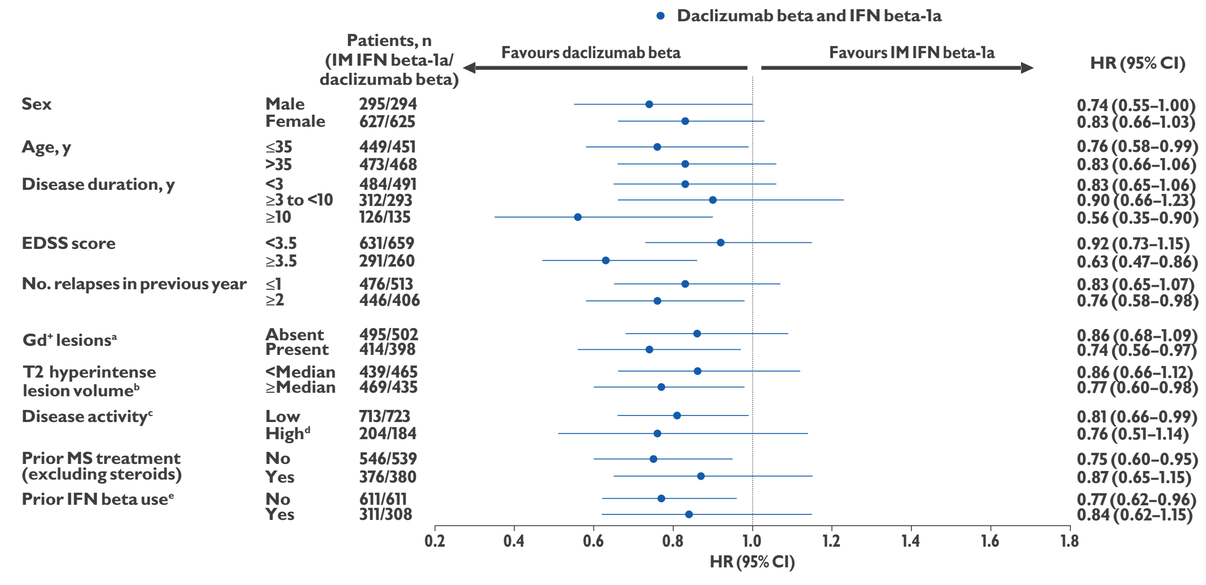
EDSS = Expanded Disability Status Scale; [a]Daclizumab beta, n=918; [b]IM IFN beta-1a, n=880; daclizumab beta, n=884; [c]IM IFN beta-1a, n=920; daclizumab beta, n=916

Figure 1. Percentage of patients who met the criteria for 24-week sustained MSFCS progression using 3 different 9HPT criteria: mean of both hands (primary analysis), either the dominant hand or the non-dominant hand and the dominant hand only



HR = hazard ratio; P values based on Cox proportional hazards model, adjusted by prior IFN beta use and and Baseline age (≤35 vs. >35 years)

Figure 2. Forest plot for 24-week sustained MSFCS progression for daclizumab beta vs. IM IFN beta-1a by Baseline demographics and disease characteristics (primary analysis)



Gd+ = gadolinium-enhancing; MS = multiple sclerosis; Time to sustained MSFCS progression was censored at Week 96 and analysed by a Cox proportional hazards model adjusted for prior IFN beta use (yes vs. no) and Baseline age (≤35 vs. >35 years), excluding covariates defining the subgroup for subgroup analyses. Subgroups with 95% CIs not crossing 1 have reached nominal significance (i.e., nominal ***P*** value <.05); [a]Missing data: IM IFN beta-1a, n=13; daclizumab beta, n=19; [b]Missing data: IM IFN beta-1a, n=14; daclizumab beta, n=19; [c]Two or more relapses but missing Baseline Gd+ data: IM IFN beta-1a, n=5; daclizumab beta, n=12. These patients were classified as missing; [d]Defined as ≥2 relapses in the year before randomisation and ≥1 Gd+ lesions at Baseline; [e]Includes IFN beta, IFN beta-1a and IFN beta-1b

CONCLUSIONS

- Daclizumab beta resulted in significantly reduced risk of 24-week sustained MSFCS progression vs. IM IFN beta-1a in the overall DECIDE population.
- The majority of patients with MSFCS progression worsened first on the SDMT, which may be a useful alternative to the PASAT-3 for detecting cognitive decline due to fewer practice effects.[1,3]
- Point estimates showed consistent trends favouring daclizumab beta over IM IFN beta-1a across several clinically important patient subgroups, supporting the treatment effects seen in the overall population.
- These results are consistent with results from subgroup analyses of daclizumab beta vs.IM IFN beta-1a on 24-week confirmed disability progression assessed using the EDSS. When taken together, these results support the efficacy of daclizumab beta on 2 distinct measures of disability progression.

References 1. Cohen JA, et al; International Advisory Committee on Clinical Trials in Multiple Sclerosis. Lancet Neurol. 2012;11(5):467-476. 2. Drake AS, et al. Mult Scler. 2010;16(2):228-237. 3. Rudick RA, et al. Mult Scler. 2009;15(8):984-997. 4. Kappos L, et al. N Engl J Med. 2015;373(15):1418-1428. 5. Benedict RH, et al. Mult Scler. 2014;20(13):1745-1752. 6. Cohan S, et al. Efficacy of daclizumab HYP vs intramuscular interferon beta-1a on disability progression across patient demographic and disease activity subgroups in DECIDE [P561]. Presented at: 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 7–10, 2015; Barcelona, Spain. **Disclosures** SC: advisory boards for Biogen, Mallinckrodt, Novartis and Sanofi-Genzyme; speaker bureaus for Acorda, Biogen, Genentech, Novartis and Sanofi-Genzyme; research support from Biogen, Genentech, Mallinckrodt, Novartis, Opexa, Roche and Sanofi-Genzyme; funds for transportation, meals and lodging from Acorda, Biogen, Mallinckrodt, Novartis and Sanofi-Genzyme; LK: institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee/consulting fees for Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB and Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi-Aventis and Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis and Teva; royalties from Neurostatus Systems GmbH; grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, Roche Research Foundations, the Swiss Multiple Sclerosis Society and the Swiss National Research Foundation; GG: advisory boards for AbbVie Biotherapeutics Inc., Biogen, Canbex, Ironwood, Novartis, Merck, Merck Serono, Roche, Sanofi-Genzyme, Synthon, Teva and Vertex; speaker fees from AbbVie Biotherapeutics Inc., Biogen, Bayer HealthCare, Genzyme, Merck Serono, Sanofi-Aventis and Teva; co-editor in chief of Multiple Sclerosis and Related Disorders; research support unrelated to study from Biogen, Genzyme, Ironwood, Merck Serono and Novartis; HW: honoraria/consulting fees from: Bayer HealthCare, Biogen, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Genzyme and Teva; grants from/contracts with Bayer HealthCare, Biogen, Deutsche Forschungsgesellschaft, the Else Kröner Fresenius Foundation, the Fresenius Foundation, the German Ministry for Education and Research, the Hertie Foundation, the Interdisciplinary Center for Clinical Studies in Münster, Germany, Merck Serono, Novartis, the NRW Ministry of Education and Research, the RE Children's Foundation, Sanofi-Genzyme and Teva; EH: honoraria/research support from Biogen, Genzyme, Merck Serono, Novartis, Roche and Teva; advisory boards for Actelion, Biogen, Genzyme, Novartis, Receptos and Teva; supported by the Czech Ministry of Education research project PRVOUK-P26/LFI/4; JR: research support from Arrien, Biogen, the Guthy Jackson Charitable Foundation, the National Multiple Sclerosis Society, Teva Neuroscience and the US Department of Veterans Affairs; member of the advisory board for the DECIDE trial, which was funded by Biogen and AbbVie Biotherapeutics Inc.; SJG: employee of and holds stock/stock options in AbbVie Inc.; GP, KR, GL and GS: employees of and hold stock/stock options in Biogen. **Acknowledgments** This study was sponsored by Biogen (Cambridge, MA, USA) and AbbVie Biotherapeutics Inc. (Redwood City, CA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Southport, CT, USA): funding was provided by Biogen and AbbVie Biotherapeutics Inc.

*Daclizumab beta, approved as ZINBRYTA®, has a different form and structure than an earlier form of daclizumab beta.