Long-term Efficacy and Safety of Daclizumab HYP in Relapsing-Remitting Multiple Sclerosis: Results From the SELECTED Extension Study

Gold R,[1] Giovannoni G,[2] Selmaj K,[3] Havrdova E,[4] Radue E-W,[5] Sprenger T,[5] Stefoski D,[6] Montalban X,[7] Riester K,[8] Greenberg SJ,[9] Ozen G,[8] Elkins J[8]

Presented by: Stanley Cohan, Providence Multiple Sclerosis Center, Portland, Oregon, USA

[1]St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [2]Queen Mary University of London, London School of Medicine and Dentistry, London, UK; [3]Medical University of Lodz, Lodz, Poland; [4]First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; [5]Medical Image Analysis Center, University Hospital Basel, Basel, Switzerland; [6]Rush University Medical Center, Chicago, IL, USA; [7]Hospital Vall d'Hebron University, Barcelona, Spain; [8]Biogen, Cambridge, MA, USA; [9]AbbVie Biotherapeutics Inc., Redwood City, CA, USA

INTRODUCTION

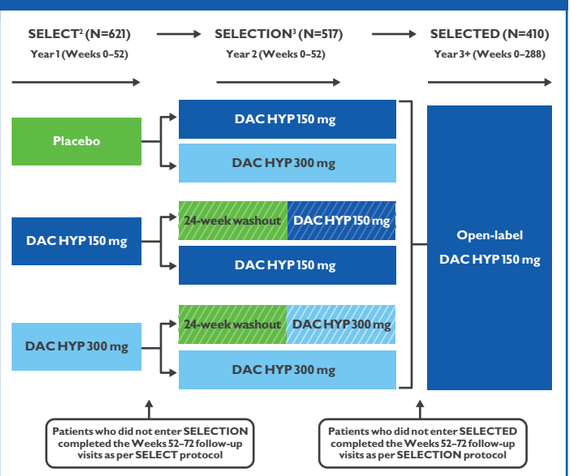
- Daclizumab high-yield process (DAC HYP) is a humanized monoclonal antibody that binds the high-affinity interleukin 2 (IL-2) receptor alpha subunit (CD25) and modulates IL-2 signaling.[1]
- The SELECT Trilogy of clinical studies was designed to evaluate the efficacy and safety of DAC HYP in patients with relapsing-remitting multiple sclerosis (RRMS; Figure 1).
- The objective of these analyses is to report interim safety and efficacy data after approximately 3 years duration of the SELECTED study.

METHODS

Study Design and Treatment

- SELECTED is an ongoing, single-arm, open-label extension study of DAC HYP 150 mg subcutaneous (SC) every 4 weeks for up to 6 years (Figure 1).

Figure 1. SELECT Trilogy study design[a]



[a]The dosing regimen for study drug (i.e., placebo or DAC HYP) was SC every 4 weeks in all 3 studies.

Analyses

- An interim analysis was performed on data collected through January 20, 2014.
- Safety results were based on data collected from the baseline visit in SELECTED (Week 52 visit in SELECTION) for all patients who enrolled and were dosed in SELECTED.
- Efficacy analyses were based on the time from first dose of DAC HYP and included the subset of SELECTED patients receiving DAC HYP 150 mg SC who had not been randomized to the washout period in SELECTION and who did not have a gap in DAC HYP 150 mg SC treatment ≥ 55 days between studies.

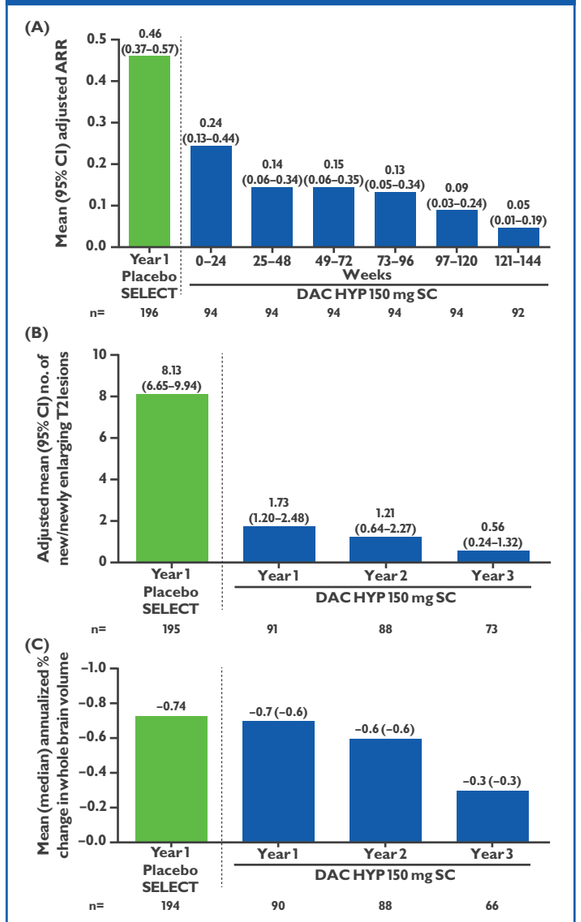
RESULTS

Patients

- The safety population consisted of 410 patients and the efficacy population 94 patients.
- At the time of this interim analysis, median time on treatment in SELECTED was 25 months (range, 0–45 months; 854 patient-years).
- Patients in SELECTED had received a median (range) of 48 (13–74) doses of DAC HYP since the start of SELECT. At the time of the interim analysis, 296 (72%) patients had received > 40 total doses and 168 (41%) had received > 50.

Efficacy Results

Figure 2. (A) Adjusted ARR by 6-month intervals; **(B)** new/newly enlarging T2 hyperintense lesions; **(C)** annualized PBVC



ARR = annualized relapse rate; PBVC = percentage brain volume change. Results from the SELECT placebo group have been published previously.[2] Adjusted ARR in SELECTED was estimated from a Poisson regression adjusted for the number of relapses in the year before study entry. Rates were estimated by time interval from the first dose of DAC HYP received. The adjusted mean number of T2 hyperintense lesions was estimated from a negative binomial regression adjusted for baseline number of T2 lesions. The annualized PBVC was determined with Structural Image Evaluation using Normalization of Atrophy (SIENA) and was calculated as percentage change divided by the number of days since the last scan multiplied by 365.25. For PBVC endpoints, patients with any post-Baseline magnetic resonance imaging assessments were included in the analysis. For all endpoints, study populations included patients for whom the time between the last dose of study treatment in the study and the first dose in the following study was < 55 days, entered in SELECTED, were treated, were still in the study at the beginning of the time interval, and were treated with DAC HYP 150 mg SC only.

Safety Overview

- The yearly incidence of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation did not increase over time and no deaths were reported (Table 1).
- Common AEs that occurred in ≥ 10% of patients were MS relapse (22%), nasopharyngitis (12%), and upper respiratory tract infection (12%).

Table 1. Overall summary of AEs

AE, n (%)	DAC HYP 150 mg SC Weeks 1–48[a] n=410	Weeks 49–96[b] n=387	Weeks 97+[c] n=279	Overall N=410
Any AE	**245 (60)**	**222 (57)**	**126 (45)**	**312 (76)**
AEs by severity				
Moderate or severe	123 (30)	126 (33)	81 (29)	211 (51)
Severe	13 (3)	11 (3)	11 (4)	33 (8)
SAE	**53 (13)**	**47 (12)**	**34 (12)**	**105 (26)**
SAE (excluding MS relapse)	**23 (6)**	**26 (7)**	**20 (7)**	**66 (16)**
AE leading to treatment discontinuation	**22 (5)**	**17 (4)**	**9 (3)**	**48 (12)**
Death	**0**	**0**	**0**	**0**

[a]Weeks 1–48 represents second year of DAC HYP treatment in patients newly treated with DAC HYP in SELECTION[3] and third year of treatment in patients originally treated with DAC HYP in SELECT.[2] [b]Weeks 49–96 represents third year of DAC HYP treatment in patients newly treated with DAC HYP in SELECTION[3] and fourth year of treatment in patients originally treated with DAC HYP in SELECT.[2] [c]Weeks 97+ represents fourth year and above of DAC HYP treatment in patients newly treated with DAC HYP in SELECTION[3] and fifth year and above of treatment in patients originally treated with DAC HYP in SELECT.[2]

Infections

- Infections were reported in 50% of patients and serious infections in 3% (Table 2). The majority of infections were mild or moderate in severity. Less than 1% of patients discontinued treatment due to infections.
  - The most common infections (≥ 10%) were nasopharyngitis (12%) and upper respiratory tract infections (12%).
  - Serious infections in ≥ 3 patients were pneumonia and urinary tract infection. DAC HYP was temporarily interrupted in 2 patients due to serious infection.

Table 2. Summary of infections, cutaneous AEs, and hepatobiliary events

AE, n (%)	DAC HYP 150 mg SC n=410
Infections	**203 (50)**
Serious infections	13 (3)
Cutaneous AEs	**115 (28)**
Serious cutaneous AEs	8 (2)
Hepatobiliary disorders	**11 (3)**
Serious hepatobiliary disorders	2 (< 1)
Hepatic laboratory abnormalities	
ALT or AST, n (%)	
≥ 3 x ULN	37 (9)
> 5 x ULN	18 (4)
> 10 x ULN	11 (3)
Elevation in ALT or AST ≥ 3 x ULN with concurrent total bilirubin > 2 x ULN	0[a]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal. [a]Two patients had elevations of ALT/AST ≥ 3 x ULN and concurrent elevations of total bilirubin > 2 x ULN that occurred 2–2.5 months after discontinuing study treatment (of which 1 occurred after the data cutoff). In both cases, other factors that could have contributed to the events were noted.

Cutaneous AEs

- Cutaneous AEs were reported in 28% of patients and serious cutaneous AEs in 2% (Table 2). In SELECT, 13% of patients in the placebo group reported cutaneous AEs over a 52-week treatment period.[2]
  - The most common cutaneous AEs were rash (7%), allergic dermatitis (5%), and eczema (3%).
  - The majority of patients who experienced cutaneous events had cutaneous events that were mild or moderate in severity; 4 (< 1%) patients had cutaneous events that were severe.
  - One serious cutaneous AE was reported as Stevens-Johnson syndrome, but the diagnosis was not supported by the case details per the central independent dermatologist and the local site dermatologist.

Hepatic AEs

- Serious hepatic AEs were observed in < 1% of patients (Table 2): 1 autoimmune hepatitis and 1 cholelithiasis.

Gastrointestinal AEs

- Six (1%) patients reported serious gastrointestinal events under the MedDRA High Level Term colitis (excluding infective) that includes ulcerative colitis (n=3), colitis, Crohn's disease, and hemorrhagic enterocolitis (each n=1).
  - Treatment included discontinuation of study treatment and standard therapies for colitis including mesalazine, sulfasalazine, corticosteroids, and azathioprine.
  - The AEs resolved or were stable with no flares following discontinuation of study treatment and/or treatment with standard therapies for colitis.

Malignancies

- There were 4 (1%) patients with malignancies: 1 each of breast cancer, basal cell carcinoma, anal cancer, and pulmonary carcinoid tumor. Based on available data, there was no evidence of an increased risk of malignancy.

CONCLUSIONS

- In these interim results, reductions in MS disease activity observed in Years 1 and 2 were maintained in Year 3 of treatment with DAC HYP 150 mg SC.
- These findings provide evidence that treatment with DAC HYP 150 mg SC over 3 years provides consistent reduction in MS disease activity.
- The safety profile of DAC HYP 150 mg SC in patients with RRMS in this interim analysis of SELECTED was comparable to that observed in SELECT[2] and SELECTION.[3]
- The risks associated with DAC HYP 150 mg SC were stable during extended treatment.
- The SELECTED study is ongoing and will provide data on up to 8 years of treatment to inform the long-term safety and efficacy profile of DAC HYP 150 mg SC monotherapy in patients with RRMS.

References

1. Wiendl H, Gross CC. *Nat Rev Neurol*. 2013;9(7):394-404.
2. Gold R, *et al*; SELECT study investigators. *Lancet*. 2013;381(9884):2167-2175.
3. Giovannoni G, *et al*; SELECTION Study Investigators. *Lancet Neurol*. 2014;13(5):472-481.

Disclosures

This study was supported by Biogen and AbbVie Biotherapeutics Inc. *RG*: consulting fees from Bayer HealthCare, Biogen, Novartis, Merck Serono, Sanofi-Aventis, and Teva; editor of *Therapeutic Advances in Neurological Disorders*; research support from Biogen, Genzyme, Merck Serono, Novartis, and Teva; *GG*: consulting fees/advisory board for AbbVie Biotherapeutics Inc., Biogen, Canbex, Ironwood, Merck, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Synthon, Teva, and Vertex; honoraria from AbbVie Biotherapeutics Inc., Biogen, Bayer HealthCare, Merck Serono, Sanofi-Aventis, and Teva; coeditor in chief of *Multiple Sclerosis and Related Disorders*; research support from Biogen, Genzyme, Ironwood, Merck Serono, and Novartis; *KS*: consulting fees from Genzyme, Novartis, Ono, Roche, Synthon, and Teva; speaker fees from Biogen; *EH*: consulting fees/advisory board and honoraria from Bayer HealthCare, Biogen, Novartis, Merck Serono, Sanofi-Genzyme, and Teva; research support from Biogen and the Czech Ministries of Education and Health (MSM 0021620849, PRVOUK-P26/LF1/4); *E-WR*: speaker fees from Actelion, Basilea, Bayer HealthCare, Biogen, Merck Serono, and Novartis; research support from Actelion, Bayer HealthCare, Biogen, Merck Serono, and Novartis; *TS*: the University Hospital Basel (employer) received funds for speaker fees/advisory board (used only for research funding) from Actelion, ATI, Biogen, ElectroCore, Genzyme, Novartis, and Mitsubishi Pharma Europe; *DS*: consulting fees from Acorda, Biogen, Serono, and Teva Neuroscience; speaker fees from Acorda, Biogen, Elan, EMD Serono, and Teva Neuroscience; royalty payments of licensed drug from Acorda; research support from Biogen, Novartis, Pfizer, and Serono; *XM*: speaker fees/travel expense reimbursement from and steering committee/advisory board for Actelion, Almirall, Bayer HealthCare, Biogen, Genzyme, Merck, Neurotec, Novartis, Octapharma, Receptos, Roche, Sanofi-Aventis, Teva, and Trophos; *SJG*: employee of and stockholder in AbbVie Biotherapeutics Inc.; *JE, GO,* and *KR*: employees of and stockholders in Biogen.

Acknowledgments

The authors acknowledge Kim Umans (Biogen, Cambridge, MA, USA), Mark Beatty, and Yaoshi Wu for their contributions to these analyses. Mark Beatty and Yaoshi Wu were full-time employees of Biogen at the time of the analyses. Biogen and AbbVie Biotherapeutics Inc. provided funding for editorial support in the development of this poster. Alison Gagnon, PhD, (Excel Scientific Solutions, Southport, CT, USA) provided editorial support. Biogen and AbbVie Biotherapeutics Inc. reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

For an electronic version of this poster, please scan code.