Interim Report on the Safety and Efficacy of Long-term Daclizumab Beta Treatment for up to 5 Years (EXTEND Trial)

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INTRODUCTION

- In controlled trials, daclizumab beta (daclizumab)* reduced clinical and radiographic evidence of disease activity vs. placebo (SELECT) and intramuscular (IM) interferon (IFN) beta-1a (DECIDE) in patients with relapsing-remitting multiple sclerosis (RRMS).[1,2]
- EXTEND is an ongoing, multicentre, open-label extension study to evaluate the safety and efficacy of long-term daclizumab beta treatment in patients with RRMS who completed DECIDE, SELECTED or OBSERVE.
  - This interim analysis includes patients enrolled into EXTEND from DECIDE.

OBJECTIVES

- To assess the long-term safety and efficacy of daclizumab beta in patients with RRMS.

METHODS

- In EXTEND, patients receive daclizumab beta 150 mg subcutaneous every 4 weeks for ≥5 years.
- EXTEND interim safety and efficacy analyses were performed using data through 13 January 2016 (patients enrolled in the pre-filled pen [PFP] substudy) or 10 September 2015 (non-PFP substudy patients).
  - Safety analyses included all patients who had ≥1 dose of daclizumab beta in DECIDE or EXTEND.
  - Relapse rate analyses included patients who completed DECIDE and enrolled in EXTEND.
  - Time to relapse and 24-week confirmed disability progression (CDP) analyses were performed for the DECIDE intention-to-treat (ITT) population in the combined DECIDE/EXTEND treatment periods.
  - Magnetic resonance imaging data through Week 48 of EXTEND are presented.

RESULTS

- In DECIDE/EXTEND, 1516 patients received daclizumab beta (exposure: 3744 patient-years; median [range], 25 [1–74] doses; Table 1).
- Most adverse events (AEs) were mild/moderate in severity; the overall incidence by treatment epoch and serious AEs (SAEs) excluding MS relapse remained stable over time (Table 1).
- Most AEs of special interest were mild/moderate in severity and the overall incidence of severe cases remained stable over time (Table 1).
- In the first 2 years of daclizumab beta treatment, the incidence of SAEs excluding MS relapse for patients switching from IM IFN beta-1a to daclizumab beta in EXTEND (Table 2) was comparable with that of daclizumab beta-treated patients in DECIDE.[2]
- During DECIDE/EXTEND, the hazard ratio (HR; 95% CI) for relapse in daclizumab beta/daclizumab beta- vs. IFN/daclizumab beta-treated patients was 0.62 (0.54–0.72; P<.0001; Figure 1A).
  - The HR (95% CI) for 24-week CDP was 0.79 (0.62–1.00; P=.047) for daclizumab beta/daclizumab beta- vs. IFN/daclizumab beta-treated patients (Figure 1B).
- In EXTEND, annualised relapse rate (ARR) decreased and lesion activity was reduced for IFN/daclizumab beta-treated patients and remained stable for daclizumab beta/daclizumab beta-treated patients (Figure 2, Figure 3).

CONCLUSIONS

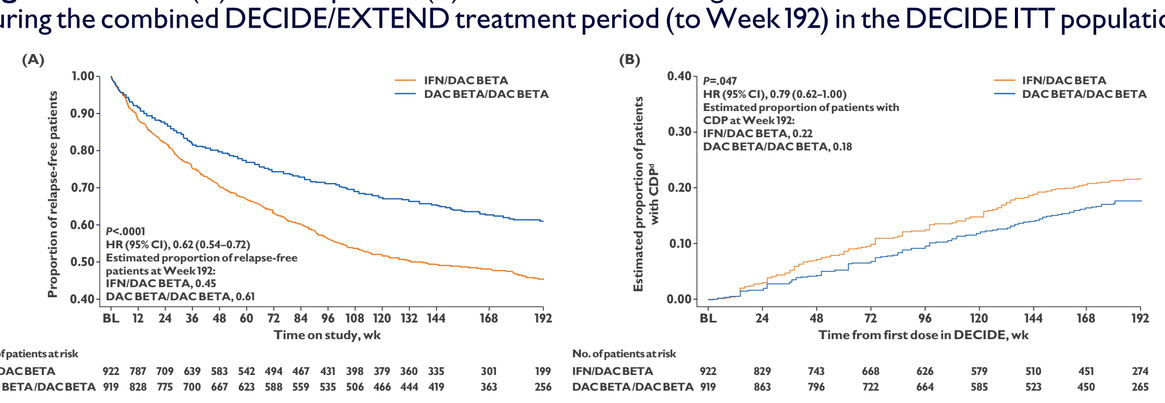
- The safety profile of daclizumab beta generally remained stable during longer-term exposure, and switching from IM IFN beta-1a to daclizumab beta was associated with comparable AE rates to those observed with daclizumab beta in DECIDE.[2]
- During EXTEND, daclizumab beta/daclizumab beta-treated patients continued to benefit from therapy, while IFN/daclizumab beta-treated patients experienced increased benefit after switching to daclizumab beta.

Table 1. Incidence and exposure-adjusted rates of treatment-emergent AEs for patients treated with daclizumab beta in the DECIDE/EXTEND combined treatment period[a,b]

Type	Weeks 1–48	Weeks 49–96	Weeks 97–144	Weeks 145–192	Overall
Patients, n	**1516**	**1397**	**808**	**618**	**1516**
Patient-years	**1349**	**1065**	**641**	**491**	**3744**
Any AE, n[c]	**1145 (84.9)**	**943 (88.5)**	**576 (89.9)**	**420 (85.6)**	**1343 (35.9)**
AEs by severity, n[c]					
Mild[d]	496 (36.8)	412 (38.7)	242 (37.8)	189 (38.5)	378 (10.1)
Moderate[d]	553 (41.0)	460 (43.2)	292 (45.6)	195 (39.8)	757 (20.2)
Severe[d]	96 (7.1)	71 (6.7)	42 (6.6)	36 (7.3)	208 (5.6)
SAEs excluding MS relapse, n[c,e]	**85 (6.3)**	**91 (8.5)**	**52 (8.1)**	**51 (10.4)**	**254 (6.8)**
Event causing treatment discontinuation, n[c]	**78 (5.8)**	**83 (7.8)**	**46 (7.2)**	**37 (7.5)**	**264 (7.1)**
AEs of special interest, n[c]					
Cutaneous AEs	257 (19.0)	225 (21.1)	145 (22.6)	125 (25.5)	550 (14.7)
Mild[d]	169 (12.5)	134 (12.6)	88 (13.7)	76 (15.5)	295 (7.9)
Moderate[d]	75 (5.6)	79 (7.4)	51 (8.0)	47 (9.6)	220 (5.9)
Severe[d]	13 (1.0)	12 (1.1)	6 (0.9)	2 (0.4)	35 (0.9)
Infection[f]	671 (49.7)	529 (49.7)	306 (47.7)	219 (44.6)	956 (25.5)
Mild[d]	372 (27.6)	314 (29.5)	173 (27.0)	124 (25.3)	459 (12.3)
Moderate[d]	279 (20.7)	198 (18.6)	124 (19.3)	88 (17.9)	448 (12.0)
Severe[d]	20 (1.5)	17 (1.6)	9 (1.4)	7 (1.4)	49 (1.3)
Lymphadenopathy	34 (2.5)	38 (3.6)	28 (4.4)	27 (5.5)	110 (2.9)
Mild[d]	22 (1.6)	21 (2.0)	17 (2.7)	16 (3.3)	64 (1.7)
Moderate[d]	12 (0.9)	13 (1.2)	9 (1.4)	10 (2.0)	38 (1.0)
Severe[d]	0	4 (0.4)	2 (0.3)	1 (0.2)	8 (0.2)
Hepatic AEs[g]	75 (5.6)	96 (9.0)	61 (9.5)	35 (7.1)	246 (6.6)

[a]For each time interval, patients were counted only once in each AE row; for the overall population, data also are included post Week 192; [b]For patients who received IM IFN beta-1a in DECIDE, this time period includes EXTEND only; [c]Numbers in parentheses are incidence rates per 100 patient-years; [d]Maximum severity of all events for each patient in the time interval; [e]SAE definitions included "required hospitalisation;" in some countries, skin biopsies were performed at a hospital and therefore met the criteria for a SAE; [f]Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class of infections and infestations; [g]Per Standardised MedDRA Query.

Figure 1. Time to (A) first relapse and (B) 24-week CDP[a] among IFN/DAC BETA- and DAC BETA/DAC BETA-treated patients during the combined DECIDE/EXTEND treatment period (to Week 192) in the DECIDE ITT population[b,c]



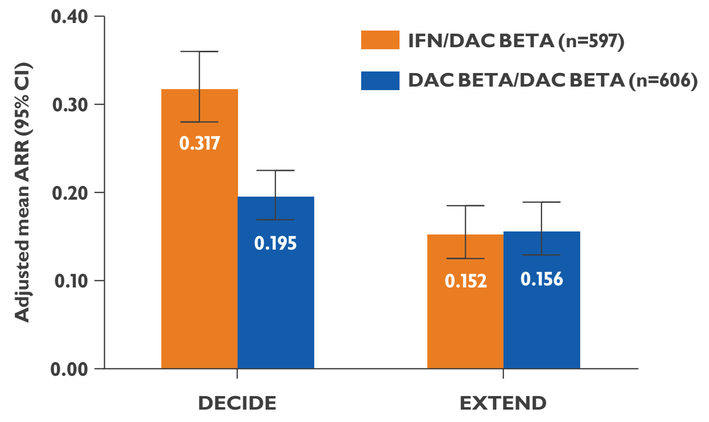
BL = Baseline; DAC BETA = daclizumab beta; [a]CDP defined as ≥1.0-point increase on Expanded Disability Status Scale (EDSS) from a DECIDE Baseline EDSS score ≥1.0 sustained for 24 weeks or ≥1.5-point increase on EDSS from a DECIDE Baseline EDSS score of 0 sustained for 24 weeks; [b]IFN/DAC BETA refers to patients who received IM IFN beta-1a in DECIDE and switched to daclizumab beta in EXTEND and patients who received IM IFN beta-1a in DECIDE and did not enrol in EXTEND. DAC BETA/DAC BETA refers to patients who received daclizumab beta in DECIDE and EXTEND and patients who received daclizumab beta in DECIDE and did not enrol in EXTEND; [c]Per study protocol, participation in DECIDE could be between 96–144 weeks according to time of enrolment[2]; [d]For patients with a tentative progression at the last EDSS assessment before the end date of the DECIDE treatment period (or the last EDSS assessment before alternative MS treatment start date) and no confirmation assessment, a multiple imputation method with logistic regression was implemented.

Table 2. Incidence and exposure-adjusted rates of treatment-emergent AEs in EXTEND for patients who received IM IFN beta-1a in DECIDE[a]

AE	Weeks 1–48	Weeks 49–96	Overall
Patients, n	**597**	**558**	**597**
Patient-years	**536**	**348**	**899**
Any AE, n[b]	**417 (77.8)**	**314 (90.2)**	**472 (52.5)**
AEs by severity, n[b]			
Mild[c]	191 (35.6)	154 (44.3)	187 (20.8)
Moderate[c]	200 (37.3)	141 (40.5)	245 (27.2)
Severe[c]	26 (4.8)	19 (5.5)	40 (4.4)
SAEs excluding MS relapse, n[b,d]	**27 (5.0)**	**26 (7.5)**	**51 (5.7)**
AE causing treatment discontinuation[b]	**27 (5.0)**	**25 (7.2)**	**52 (5.8)**

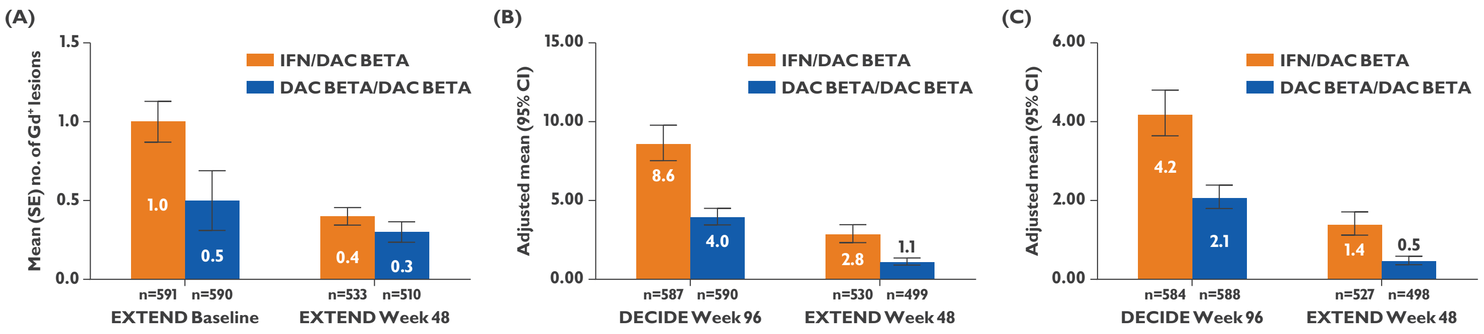
[a]For each time interval, patients were counted only once in each AE row; [b]Numbers in parentheses are incidence rates per 100 patient-years; [c]Maximum severity of all events for each patient in the time interval; [d]SAE definitions included "required hospitalisation;" in some countries, skin biopsies were performed at a hospital and therefore met the criteria for a SAE.

Figure 2. ARR[a] for IFN/DAC BETA- and DAC BETA/DAC BETA-treated patients in DECIDE and EXTEND treatment periods[b]



[a]Estimated from a negative binomial regression model adjusted for the following characteristics at DECIDE Baseline: Baseline relapse rate, prior IFN beta use, Baseline EDSS score (≤2.5 vs. >2.5) and Baseline age (≤35 vs. >35 years); [b]IFN/DAC BETA refers to patients who received IM IFN beta-1a in DECIDE and switched to daclizumab beta in EXTEND. DAC BETA/DAC BETA refers to patients who received daclizumab beta in DECIDE and EXTEND.

Figure 3. (A) Gd+ lesions at Baseline and Week 48a; (B) no. of newT2 hyperintense lesions at Week 48b; and (C) no. of new T1 hypointense lesions at Week 48b for IFN/DAC BETA- and DAC BETA/DAC BETA-treated patients in EXTEND



Gd+ = gadolinium enhancing; [a]Data are shown for the number of Gd+ lesions at enrolment in EXTEND (Baseline) and at Week 48 of EXTEND; [b]For DECIDE, data are shown for the number of new T2 hyperintense and T1 hypointense lesions at Week 96 relative to DECIDE Baseline (note: some patients in DECIDE continued on treatment up to Week 144). Values in this analysis were estimated from a negative binomial regression model using data from the EXTEND ITT population. The model included prior treatment group in DECIDE and is adjusted for the following characteristics: volume of T2 hyperintense/T1 hypointense lesions, prior IFN beta use and age (≤35 vs. >35 years) at DECIDE Baseline. For EXTEND, data are shown for the number of new T2 hyperintense and T1 hypointense lesions at Week 48 relative to EXTEND Baseline. Values were estimated from a negative binomial regression model. The model included prior treatment group in DECIDE and is adjusted for the following characteristics: volume of T2 hyperintense/T1 hypointense lesions, prior IFN beta use and age (≤35 vs. >35 years) at EXTEND Baseline

References 1. Gold R, *et al*; SELECT study investigators. *Lancet*. 2013;381(9884):2167-2175; 2. Kappos L, *et al. N Engl J Med*. 2015;373(15):1418-1428. **Disclosures** LK: institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee for and consulting fees from 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; SC: advisory boards for Biogen, Genzyme, Mallinckrodt and Novartis; speaker bureaus for Acorda, Biogen, Genentech, Genzyme and Novartis; research support from Biogen, Genentech, Genzyme, Mallinckrodt, Novartis, Opexa and Roche; DLA: honoraria from Bayer HealthCare, Biogen, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, Merck Serono, Novartis, Roche and Teva; employee of and stockholder in NeuroRx Research; OM, PM and GL: employees of and hold stock/stock options in Biogen; SJG: employee of and holds stock/stock options in AbbVie Inc. **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.