Reversible Effects of Daclizumab Beta on Lymphocyte Counts in RRMS Patients: Data From the SELECT Trilogy Studies

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P211

INTRODUCTION

- Daclizumab beta (DAC BETA)* is a humanised monoclonal antibody against the interleukin 2 receptor alpha subunit (CD25) in late-stage clinical development for the treatment of relapsing-remitting multiple sclerosis (RRMS).[1,2]
- DAC BETA selectively modulates interleukin 2 receptor signalling, leading to selective antagonism of proinflammatory effector T cell activity and increased numbers of immunoregulatory CD56^{bright} natural killer (NK) cells.[1,2]

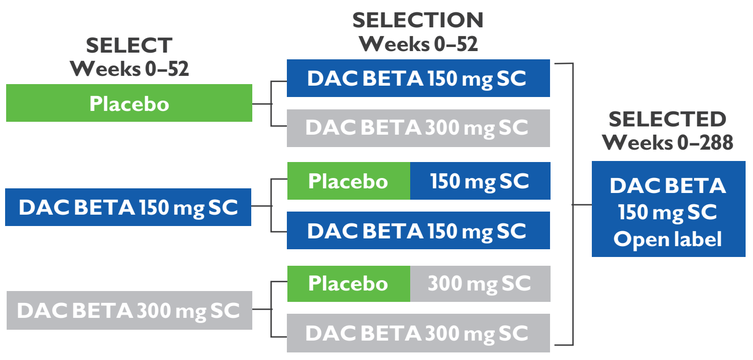
OBJECTIVES

- To evaluate the effects of DAC BETA 150 mg on total and differential lymphocyte populations in patients with RRMS.

METHODS

- SELECT was a multicentre, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of DAC BETA in patients with RRMS.[3] Patients received placebo or DAC BETA subcutaneously (SC) every 4 weeks at a dose of 150 mg or 300 mg.[3] Data from patients randomised to receive the 150-mg dose are presented here.
- SELECTION was a randomised double-blind extension study. Patients in the DAC BETA groups who completed SELECT and enrolled in SELECTION were randomised to continue DAC BETA or to discontinue treatment for 24 weeks before reinitiating therapy[4] (Figure 1).

Figure 1. SELECT Trilogy study design

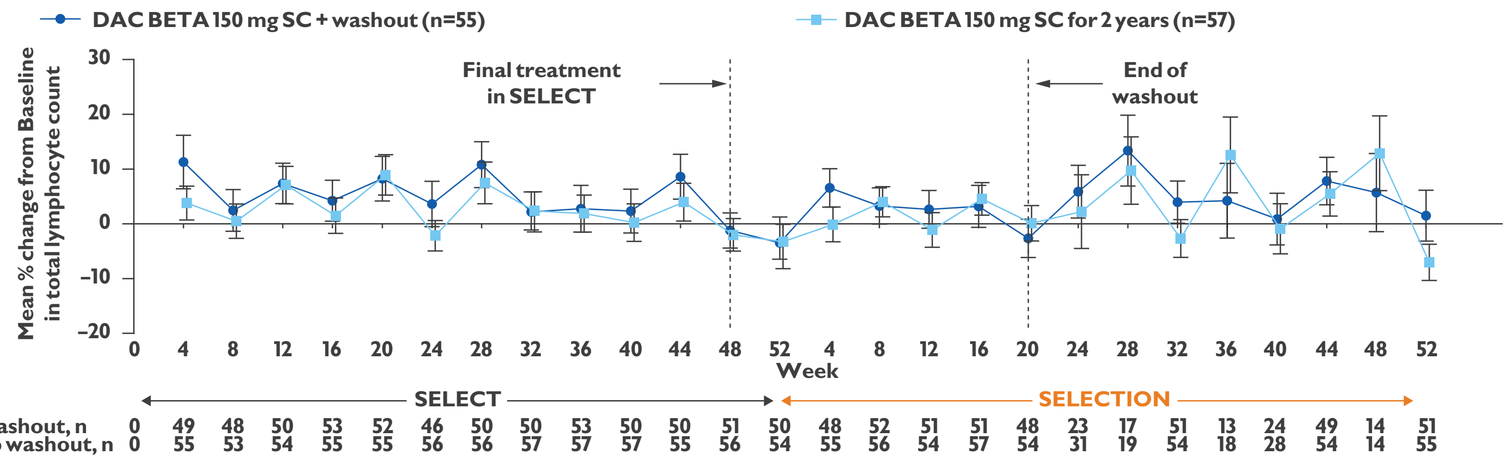


- Blood samples were obtained at Baseline and every 4 weeks thereafter for assessment of total lymphocyte count. Differential cell counts were assessed at Baseline; Weeks 4, 8, 16, 24, 32, 48 and 52 of SELECT; every 4 weeks during the washout period; and Week 52 of SELECTION.
- Total and differential lymphocyte counts (CD3$^+$CD4$^+$ and CD3$^+$CD8$^+$ T cells, CD56^{bright} NK cells [CD3$^-$CD16$^+$CD56^{bright}] and regulatory T [Treg] cells [CD4$^+$CD127$^{low/-}$FOXP3$^+$]) were assessed at multiple time points using validated flow cytometry assays in patients who received DAC BETA 150 mg SC in SELECT and SELECTION.
- Of the patients who completed SELECTION and had >1 biomarker measurement (washout, n=73; no washout, n=76), those with >55 days between their final treatment in SELECT and first treatment in SELECTION were excluded from the analysis.

RESULTS

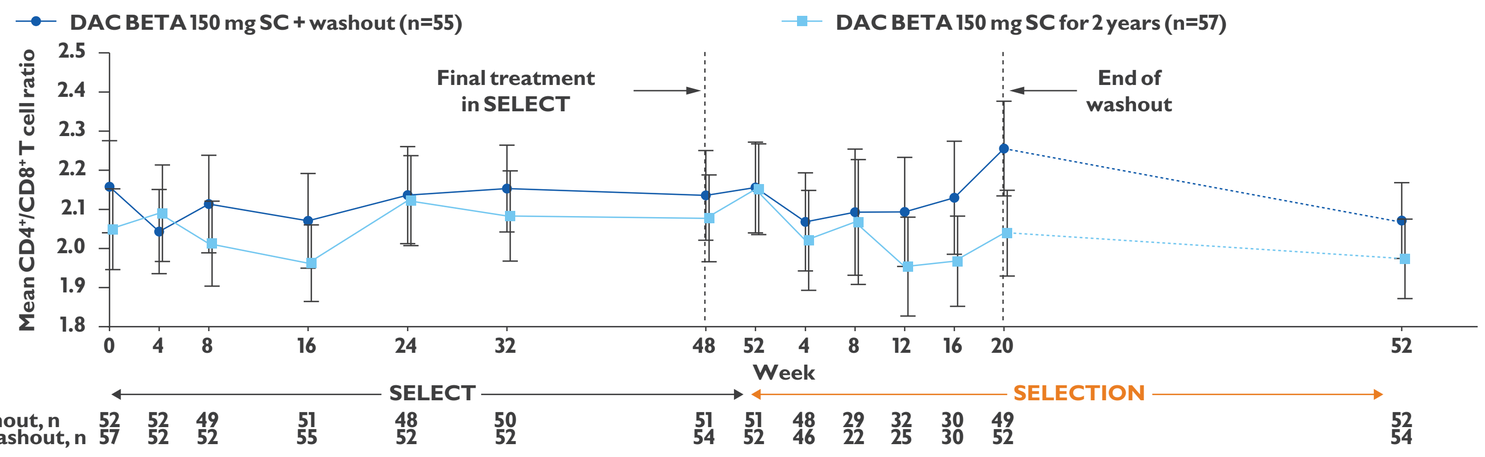
- Fifty-five patients randomised to a 24-week washout period and 57 patients randomised to continue DAC BETA 150 mg SC for 2 consecutive years in SELECTION were included in this analysis.
- At the end of the washout period, mean total lymphocyte counts were not notably different from Baseline. The mean CD4$^+$/CD8$^+$ T cell ratio remained stable throughout SELECT and SELECTION (range, 2.0–2.3; Figures 2 and 3).
- Mean CD4$^+$ and CD8$^+$ T cell counts decreased modestly from Baseline over 52 weeks of treatment with DAC BETA 150 mg SC and were not notably different from SELECT Baseline values during and at the end of the washout period (Week 20 of SELECTION; Figure 4).
- Among all patients who completed SELECTION and for whom biomarkers were measured (washout, n=73; no washout, n=76), CD56^{bright} NK cell counts exhibited ~5-fold expansion by Week 52 of SELECT, while Treg cells declined by 58.4% (median; mean reduction, 43%) from Baseline. Mean CD56^{bright} NK and Treg cell counts returned to SELECT Baseline values by the end of the washout period, as shown in Figure 5 for patients with ≤55 days between SELECT and SELECTION.
- In patients receiving 2 years of continuous treatment with DAC BETA 150 mg SC, the increase in CD56^{bright} NK cells and reductions in Treg, CD4$^+$ and CD8$^+$ cells reached a plateau at the end of Year 1 and did not progress indefinitely.

Figure 2. Mean percentage change from Baseline in total lymphocyte count



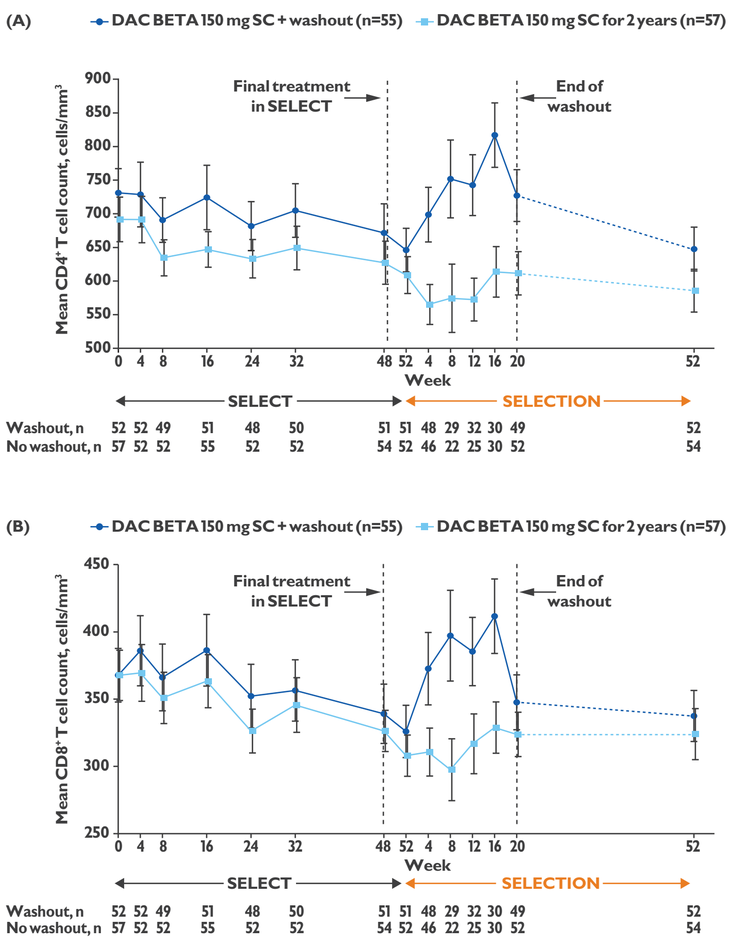
Error bars represent standard error of the mean (SEM)

Figure 3. Mean CD4$^+$/CD8$^+$ T cell ratio over SELECT and SELECTION



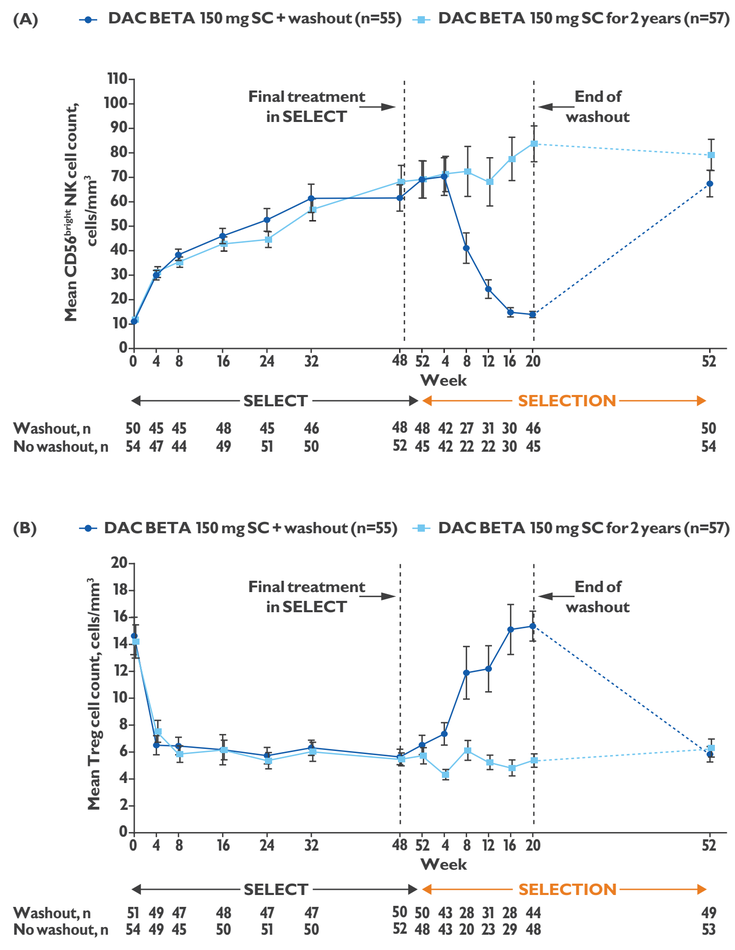
Error bars represent SEM. Differential cell count data not available between Weeks 20 and 52 of SELECTION

Figure 4. Mean **(A)** CD4$^+$ and **(B)** CD8$^+$ T cell counts over SELECT and SELECTION



Error bars represent SEM. Differential cell count data not available between Weeks 20 and 52 of SELECTION

Figure 5. Mean **(A)** CD56^{bright} NK and **(B)** Treg cell counts over SELECT and SELECTION



Error bars represent SEM. Differential cell count data not available between Weeks 20 and 52 of SELECTION

CONCLUSIONS

- Decreases in total and differential lymphocyte counts during DAC BETA treatment were modest and reversible upon treatment discontinuation. Total lymphocyte counts returned to Baseline levels ~8–12 weeks after the last dose of DAC BETA. The CD4$^+$/CD8$^+$ ratio remained stable in SELECT and SELECTION.
- Consistent with prior observations, initiation of DAC BETA led to a rapid expansion in CD56^{bright} NK cells and a reduction in Treg cells from Baseline levels, both of which were reversible within 24 weeks after suspension of DAC BETA.
- The absence of profound depletion of total lymphocytes and CD4$^+$ and CD8$^+$ T cells during treatment and the reversibility of the changes in cell counts examined provide further evidence of the targeted immunomodulatory mechanism of action of DAC BETA in MS.

References 1. Wiendl H, Gross CC. *Nat Rev Neurol*. 2013;9(7):394-404. 2. Elkins J, *et al. Neurol Neuroimmunol Neuroinflamm*. 2015;2(2):e65. 3. Gold R, *et al.*; SELECT study investigators. *Lancet*. 2013;381(9884):2167-2175. 4. Giovannoni G, *et al.*; SELECTION Study Investigators. *Lancet Neurol*. 2014;13(5):472-481. **Disclosures** SF, OM, DM, KR, PM and JE: employees of and hold stock/stock options in Biogen; JS: employee of and holds stock/stock options in AbbVie Biotherapeutics 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.