Safety in the CARE-MS II Core and Extension Studies, and TOPAZ Study Through 8 Years

- The incidence of adverse events (AEs) in general was reduced in Years 3–8 compared with the core study (Years 1–2), and declined over time
  - The incidence of infections declined from Years 4–8; the incidence of serious infections was ≤3.3% per year through 8 years
  - Thyroid AE incidence peaked in Year 3, as reported previously, and declined subsequently through Year 8; cumulative incidence in Years 1–8 was 43.7% for thyroid AEs and 5.1% for serious thyroid AEs
  - No immune thrombocytopenia (ITP) events occurred after the 48-month monitoring period following the last alemtuzumab dose; there were no new events in Year 8
  - No new autoimmune nephropathy cases occurred in Year 8
  - 10 malignancy cases were reported over 8 years: 2 thyroid cancers, 2 basal cell carcinomas, 2 malignant melanomas in situ, 1 B-cell lymphoma, 1 squamous cell carcinoma, and 1 breast cancer (all assessed by the sponsor as not related to alemtuzumab); 1 basal cell carcinoma (assessed by the sponsor as possibly related to alemtuzumab)

- In Year 6, 1 patient experienced cerebral hemorrhage and recovered
- The most commonly reported AEs were infusion-associated reactions (IARs), which declined after the first course of alemtuzumab (Course 1: 83.7%; Course 2: 71.5%; Course 3: 62.0%; Course 4: 64.7%)
  - The incidence of serious IARs was low (Course 1: 1.4%; Course 2: 1.4%; Course 3: 1.0%; Course 4: 1.2%)
  - 6 deaths were reported in patients from CARE-MS II who entered TOPAZ (Years 7–8)
    - 2 deaths occurred in Year 7 and were reported previously (suicide [n=1], unknown cause [n=1]; results of the autopsy were not provided); assessed by both the sponsor and investigators as not related to alemtuzumab
    - 4 deaths were reported in Year 8, which were assessed by the sponsor and investigators as not related to alemtuzumab (sudden death [without autopsy], suicide, acute/organizing bronchopneumonia, and atrioventricular block, reported approximately 78, 30, 17, and 26 months after the last alemtuzumab dose, respectively)

Additional Information Regarding Safety in Post-Marketing Use

- Post-marketing frequencies are not directly comparable to clinical trial incidences because of differences in ascertainment methodology and follow-up duration, and limitations of post-marketing reporting
  - Post-marketing reports may include non-serious cases, inaccurate diagnoses, and duplicate cases; most cases cannot be confirmed, the level of clinical detail available is often limited, and cases are subject to under-reporting
  - The sponsor performs ongoing evaluation of post-marketing safety reports from multiple sources to refine understanding of the safety and benefit:risk profile of alemtuzumab and to identify potential new safety signals
  - Engagement with health authorities occurs to ensure that alemtuzumab labels are updated to incorporate new information when clinically relevant: