Pregnancy Outcomes in Alemtuzumab-Treated RRMS Patients

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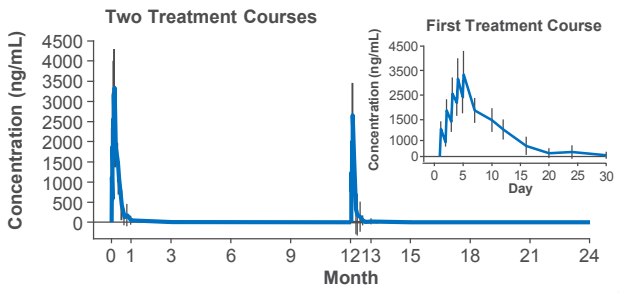
OBJECTIVE

- **To provide an update on pregnancy outcomes in female alemtuzumab-treated patients in the phase 2 and 3 clinical development program as of 1st April 2017**

INTRODUCTION

- In phase 2 and 3 studies of patients with active RRMS, alemtuzumab-treated patients demonstrated greater improvements in clinical and MRI outcomes versus SC IFNB-1a (NCT00050778; NCT00530348; NCT00548405)[1-3]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[1-3]
- Alemtuzumab-treated patients who were followed up for an additional 4 years in an extension study (NCT00930553) continued to show efficacy over time, even though most patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT)[4-8]
- The effects of alemtuzumab over time may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[9,10]
  - Following depletion, a relative increase of regulatory T cells and a decrease in proinflammatory cytokines occur, potentially leading to a rebalancing of the immune system[11,12]
  - The exact mechanism of action of alemtuzumab is not fully elucidated
- Patients completing the extension study could enroll in the 5-year TOPAZ study (NCT02255656) for further evaluation
- It is important to assess the effects of DMTs on pregnancy, since MS is frequently diagnosed in women of childbearing age
- Murine studies of alemtuzumab suggest placental transfer and pharmacologic activity in pups exposed during gestation and postpartum, and reduced fetal viability at high concentrations[13]
  - Development was not affected in pups exposed during lactation
- In humans, alemtuzumab is low or undetectable in serum within approximately 30 days after administration (**Figure 1**)[14]
- It is recommended that women of childbearing potential use contraception during and for 4 months after treatment to reduce the likelihood of exposure to the fetus[13]

Figure 1. Mean Serum Alemtuzumab Concentration Over Time After Dosing 12 mg/day at Months 0 and 12[14]



METHODS

Study Design

- Alemtuzumab was evaluated in 3 randomized, rater-blinded, active-controlled studies: the 3-year, phase 2 CAMMS223 study and the 2-year, phase 3 CARE-MS studies[1-3]
  - Patients received annual courses of alemtuzumab 12 mg (or 24 mg in CAMMS223 and CARE-MS II)
- Courses consisted of IV infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later, and 24 months later in a minority of patients in the CAMMS223 study
- In the extension study, patients could receive additional treatment with alemtuzumab (12 mg on 3 consecutive days ≥1 year after the most recent course) as needed for relapse or MRI activity, or other licensed DMTs at the investigator's discretion[4-8]
- Patients enrolling in TOPAZ can receive additional courses of alemtuzumab (12 mg on 3 consecutive days) ≥12 months after the most recent course or other DMT at any time point, both per investigator discretion (no criteria)[15]

Safety

- To prevent exposure to a fetus, a pregnancy test was required in females of childbearing potential prior to each course of alemtuzumab
- Patients were required to use an effective method of contraception during the core studies, and in the extension for 6 months following each alemtuzumab treatment course
- Patients who became pregnant could remain in the studies for safety follow-up, but further administration of alemtuzumab was not permitted in patients who were pregnant or lactating

Analysis

- Pregnancy outcomes were derived from safety reporting as of 1st April 2017; baseline characteristics and relative risks of spontaneous abortion by maternal age and by time since last alemtuzumab dose were derived from the clinical database with a cutoff date of October 2016
- Fisher's exact test was used to test for significance of the relative risks of spontaneous abortion by maternal age and by time of pregnancy onset since last alemtuzumab dose

CONCLUSIONS

- **Normal live births have been the most common outcome in women exposed to alemtuzumab in clinical studies**
  - **There is no evidence of an increased risk for congenital anomalies or birth defects in live-delivered infants**
- **Spontaneous abortion rate in alemtuzumab-treated patients is comparable to rates in the general population[19] and treatment-naive MS patients[20-23]**
- **Based on pharmacokinetics of alemtuzumab and label recommendations, women of childbearing potential should continue to use contraception for 4 months after receiving a course of alemtuzumab**
- **In the postmarketing setting, the International Alemtuzumab Pregnancy Exposure Registry is open for patients who become pregnant within 4 months after an infusion of alemtuzumab**

RESULTS

Pregnancy Outcomes in Alemtuzumab-Treated Female Patients in the Clinical Development Program

- As of 1st April 2017, 248 pregnancies occurred in 156 of 972 female patients treated with alemtuzumab (**Table 1**), including 218 known outcomes with 147 live births
- Of the 147 live births:
  - No congenital anomalies or birth defects were observed
  - Five infants were born prematurely (range, 31–36 weeks)

Table 1. Pregnancy Outcomes in Female Patients Treated With Alemtuzumab 12 or 24 mg

Outcomes	N=972
All pregnancies, n	248
Completed pregnancies with known outcomes, n (%)	218 (87.9)
Ongoing[a]	14 (5.6)
Outcome unknown	16 (6.5)
Known outcomes in completed pregnancies, n	218
Live births, n (%)	147 (67.4)
Spontaneous abortion[b]	48 (22.0)
Elective abortion	22 (10.1)
Stillbirth[c]	1 (0.5)

[a]As of 1st April 2017; [b]<20 weeks' gestation; [c]≥20 weeks' gestation

- Elective abortions (n=22; 10%) were due to personal choice (n=6), extrauterine pregnancy (n=3), anembryonic gestation (n=2), chromosomal abnormality (n=2), or fetal defect (n=1; cystic hygroma and hypoplastic heart occurring 26 months after the last alemtuzumab dose); 8 had no information available
- There was 1 stillbirth, owing to nuchal cord and amniotic band syndrome with abnormalities of the left hand[16]
  - Fetal demise occurred at 38 weeks and 4 days' gestation and was 4 years after the last alemtuzumab dose
- Spontaneous abortion rate was 22%
  - Maternal age was associated with increased spontaneous abortion rates in alemtuzumab-treated patients
    - Patients <35 years, 15% (22/148)
    - Patients ≥35 years, 37% (26/70)
    - Relative risk, 2.50 (95% CI:1.53, 4.08), *P*=0.0003
    - Approximate rates in the general population: 15%–23% for women 20–35 years; 23%–83% for women 36–45 years[17]
- Mean age at conception in the alemtuzumab-treated patients was 32.5 years (median, 33 years; range, 21–44; **Table 2**)
  - Mean time from previous dose to conception was almost 3 years

Table 2. Characteristics of Pregnant Patients

Characteristics	(n=248)
Age at conception, years	32.5 (4.4)[a]
Age of patients <35 years	30.2 (3.3)[a]
Age of patients ≥35 years	37.4 (2.0)[a]
Caucasian race, n (%)	143 (92)[b]
Years from first relapse to conception	7.5 (2.8)[a]
Years from last relapse to conception	3.7 (2.6)[a]
Time from previous alemtuzumab dose to conception, months	33.5 (22.6)[a] range, 0.30–106.7
Last EDSS score prior to conception	1.6 (1.3)[a] range, 0–6.5

Values shown are mean (SD) except where stated
[a]n=248; based on pregnancy occurrences during the study; multiple pregnancies are counted distinctly
[b]n=156; based on the number of patients with a pregnancy event

- Of the 248 pregnancies, 232 occurred >4 months after the last alemtuzumab dose (ie, after the period for contraception use recommended in the drug label; **Table 3**)
  - 16 pregnancies occurred ≤4 months after alemtuzumab treatment, resulting in 8 live births with no birth defects; 1 infant had respiratory distress syndrome and 1 infant had Grade 4 thyrotoxic crisis 3 weeks after birth, attributable to maternal Graves' disease[16]
    - In this cohort, there were 3 spontaneous abortions (1 related to ectopic pregnancy), 4 elective abortions, and 1 ongoing pregnancy
  - Risk of spontaneous abortion was not increased in patients becoming pregnant ≤12 months after alemtuzumab exposure (11%) compared with those becoming pregnant >12 months since alemtuzumab exposure (25%; relative risk, 0.46 [95% CI: 0.19–1.09], *P*=not significant)

Table 3. Pregnancy Outcomes by Time Since Last Alemtuzumab Dose

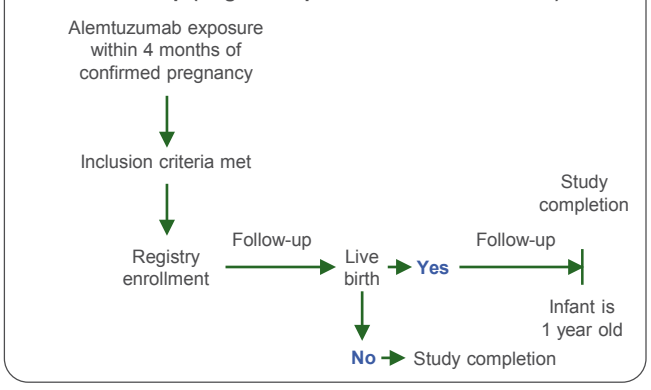
	Number of Months From Last Alemtuzumab Dose to Pregnancy Onset			
	≤1 Month	>1 to ≤4 Months	>4 to ≤12 Months	>12 Months
Pregnancies, n	5	11	31	201
Outcome, n				
Live birth	2	6	22	117
Ongoing[a]	1	–	1	12
Elective abortion	2	2	5	13
Spontaneous abortion[b]	–	3	2	43
Stillbirth[c]	–	–	—	1
Unknown	–	–	1	15

[a]As of 1st April 2017; [b]<20 weeks' gestation; [c]≥20 weeks' gestation

Postmarketing Data Collection of Real-World Pregnancy Outcomes in Alemtuzumab-Treated Patients

- In the postmarketing setting, real-world data are currently being collected by the International LEMTRADA® Pregnancy Exposure Registry, a prospective, noninterventional, observational safety study (**Figure 2**)[18]
- Primary objective
  - To evaluate pregnancy outcomes in women with MS who became pregnant within 4 months after alemtuzumab exposure, and to determine if the risk of any adverse pregnancy outcomes in these women is higher compared with external cohorts of women with MS who have not been exposed to alemtuzumab during pregnancy, as well as pregnant women without MS
- Secondary objective
  - To further characterize prenatally exposed live births including assessment of outcomes in the neonatal and pediatric periods for up to 1 year of age (pending available data)
- **Physicians in the UK wishing to enroll patients in the LEMTRADA® Pregnancy Exposure Registry should contact the National Coordinating Centre (Manchester, UK)**
  - **Phone: 0161 206 0534; Email: Neuroresearch.nurse@srft.nhs.uk**

Figure 2. Registry Design[18]



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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

TOPAZ=a long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study

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Alemtuzumab is approved in >70 countries around the world for treatment of adults with relapsing forms of multiple sclerosis (MS). In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. This material may contain information that is outside of the approved labeling in some countries.

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