

Pregnancy Experience: Nonclinical Studies and Pregnancy Outcomes in the Daclizumab Clinical Study Program

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ABSTRACT

Introduction: Multiple sclerosis (MS) is more common in women and can occur during childbearing years; thus, information on outcomes following exposure to MS therapy during pregnancy is important. No formal

studies of daclizumab have been conducted in pregnant women. Here, we report available nonclinical and clinical data on pregnancy outcomes from the daclizumab clinical study program.

Methods: Reproductive and developmental toxicity studies were conducted in cynomolgus monkeys. Reports of pregnancies that occurred during the daclizumab clinical study program through March 9, 2015 were collated and summarized. In the event of pregnancy, daclizumab was discontinued and safety monitoring continued.

Results: Studies in cynomolgus monkeys showed no daclizumab-related effects on maternal well-being, embryo–fetal development, indirect fertility end points, and pre- and postnatal development and growth. Across the clinical study program, 38 pregnancies were reported in 36 daclizumab-exposed women (on treatment ≤ 6 months from last dose); 20 resulted in live births and four (11%) in spontaneous abortions or miscarriages. One congenital heart defect (complex transposition of great vessels) occurred in one live birth (considered unrelated to daclizumab); daclizumab had been discontinued and intramuscular interferon beta-1a and

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lisinopril were used at conception. Eight women had an elective termination, two had an ectopic pregnancy, and two were lost to follow-up; two pregnancy outcomes are pending. Six additional pregnancies occurred in five women >6 months after their last daclizumab dose; in one additional pregnancy, exposure was unknown.

Conclusion: Spontaneous abortion rate in daclizumab-exposed women was consistent with early pregnancy loss in the general population (12%–26%). Data on pregnancies exposed to daclizumab do not suggest an increased risk of adverse fetal or maternal outcomes, although the numbers are too small for definitive conclusions.

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INTRODUCTION

The diagnosis of multiple sclerosis (MS) occurs more frequently in women than men, with a peak incidence during childbearing age, making it important to understand the effects of disease-modifying therapy (DMT) exposure on pregnancy [1]. In clinical practice, many European physicians prescribe DMTs up to the time of conception to avoid the risk of disease reactivation during withdrawal, with the advice to cease therapy once pregnancy is confirmed [1]. In the USA, it is more common to recommend this clinical pathway only for patients with highly active disease [2]. Thus, data on exposure risks during pregnancy, delivery, and postpartum are usually reported

from retrospective post-marketing follow-up or unplanned pregnancies in controlled clinical studies.

Daclizumab high-yield-process (daclizumab)¹ is a humanized monoclonal antibody with a novel mechanism of action compared with other DMTs. Daclizumab binds to the high-affinity interleukin 2 (IL-2) receptor, resulting in attenuation of proinflammatory activated T cell responses, and substantial expansion and stimulation of immune regulatory CD56^{bright} natural killer (NK) cells, which penetrate the blood–brain barrier where it has been postulated that they lyse activated T cells, leaving resting T cells intact [3, 4]. Together, these immunomodulatory effects are believed to reduce central nervous system pathology in MS, decreasing relapses and disability progression. Interestingly, elevated circulating CD56^{bright} NK cells also are associated with decreased MS relapse rate in pregnancy during the third trimester [5]. Also noteworthy is that while uterine CD56^{bright} NK cells are known to be involved in successful fetal implantation and placental maturation, the phenotype differs from the peripheral cells [6].

The nonclinical toxicology program was designed to support the chronic subcutaneous (SC) administration of daclizumab in relapsing forms of MS. Daclizumab binds to cynomolgus monkey CD25 and dose-dependently blocks IL-2-dependent proliferation of effector T cells, but does not bind to the analogous rat or murine protein (AbbVie Biotherapeutics Inc., data on file). Human and cynomolgus monkey CD25 share 92% sequence identity and daclizumab binds with similar affinity to recombinant human and cynomolgus monkey

¹ Daclizumab high-yield process, approved as ZinbrytaTM, has a different form and structure than an earlier form of daclizumab (Zenapax).

CD25 proteins (AbbVie Biotherapeutics Inc., data on file). Cynomolgus monkeys also have been used to investigate the effects of CD25-blocking antibodies in other models of disease, including collagen-induced arthritis and autoimmune uveitis [7, 8]. These in vitro and in vivo data underpinned the use of the cynomolgus monkey as a pharmacologically relevant species for toxicology studies where daclizumab was evaluated for its potential effects on male and female fertility, embryo–fetal development, and pre- and postnatal development and growth.

The efficacy and safety findings for daclizumab in patients with relapsing MS have been reported from a large placebo-controlled monotherapy registrational study [SELECT (Clinicaltrials.gov identifier: NCT00390221)], as well as the subsequent extension studies [SELECTION (NCT00870740), SELECTED (NCT01051349)], and from a large active-controlled [intramuscular (IM) interferon beta-1a] monotherapy phase III study [DECIDE (NCT01064401)] [9–13]. Comparative clinical data from patients with relapsing MS in DECIDE showed that daclizumab 150 mg SC every 4 weeks was superior to interferon beta-1a 30 mcg/week IM across a number of clinical, magnetic resonance imaging, patient-reported, and functional (e.g., cognitive) outcomes in the overall study population, as well as in various patient subgroups, and with a tolerability profile largely reflective of its mechanism of action [11]. In general, the majority of adverse events seen with daclizumab were mild or moderate in intensity. Hepatic events, skin reactions, and infections were observed at a higher incidence with daclizumab than IM interferon beta-1a in DECIDE [11]; however, rates did not appear to increase over time [14]. Long-term data from the SELECT Trilogy of studies showed that daclizumab 150 mg efficacy continued over a

3-year period, with no evidence of accumulated toxicity [9, 10, 12]. Formal studies of daclizumab in pregnancy have not been conducted.

This report describes pregnancy outcomes in patients with unintentional pregnancies that occurred in the daclizumab clinical study program as well as the nonclinical study results.

METHODS

Nonclinical

All the nonclinical studies, except the pre- and postnatal study, utilized daclizumab SC, which was formulated as follows: 100 mg/mL daclizumab in vehicle (40 mM succinate buffer, 100 mM sodium chloride, and 0.03% Tween 80, pH 6.0). For the pre- and postnatal study, daclizumab was formulated in the same buffer, but at 150 mg/mL. Control animals received the vehicle. All studies were conducted in compliance with Good Laboratory Practice regulations using material representative of, or identical to, the lots of drug substance used in the production of the clinical drug. The reproductive and developmental toxicity studies included toxicokinetic assessments. Fetal exposure was determined in an embryo–fetal study by analysis of umbilical cord fluid levels at cesarean delivery, and the pre- and postnatal study included measurements of daclizumab in maternal and offspring serum, and maternal milk. The presence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) was assessed in all studies.

Male Fertility Study

Groups of eight (0 and 200 mg/kg) and five (10 and 50 mg/kg) sexually mature male cynomolgus monkeys, 5.0–10.5 years of age, received daclizumab once every 2 weeks for

~60 days (to cover a complete spermatogenesis cycle). One week following the final dose (fifth dose, day 64), five animals per group were necropsied; three animals in the control and 200-mg/kg groups remained on study for a 12-week postdose recovery period to assess the reversibility of any potential daclizumab-related effects. Male reproductive capacity was assessed indirectly via sperm analysis (counts, motility, and morphology) and serum testosterone levels, which were evaluated twice pre study, twice during dosing, and at the end of the recovery period. A full histopathology evaluation that included male reproductive tract tissues was conducted.

Female Fertility Study

Groups of eight (0 and 200 mg/kg) or five (10 and 50 mg/kg) sexually mature female monkeys received daclizumab once every 2 weeks for five doses. Dosing was synchronized with each animal's menstrual cycle. Animals were dosed over approximately two menstrual cycles, followed by an 8-week postdosing recovery period. Five animals per group were euthanized on days 92–94 (35–37 days post dosing). Three animals from the control and the 200-mg/kg groups were continued on study and euthanized on days 120–123, following a ~60-day postdose recovery period to assess the reversibility of any potential daclizumab-related effects. Female reproductive capacity was assessed indirectly by changes in menstrual cycle and ovarian function (assessed by estradiol and progesterone levels during the follicular and luteal phases of the menstrual cycle). Full necropsy and histological evaluation was performed at the end of the study, including reproductive tract tissues and adrenal and pituitary glands.

Embryo–Fetal Developmental Study

Groups of 12 (50 mg/kg), 13 (0 and 10 mg/kg), and 15 (200 mg/kg) pregnant monkeys received daclizumab (0, 10, 50, or 200 mg/kg) during the period of organogenesis [i.e., ≤ 2 days of confirmed pregnancy; gestation day (GD) 20–22] and weekly thereafter through GD50 for five doses. All adult females underwent cesarean delivery on $GD100 \pm 2$. Fetal evaluations were conducted and consisted of external and visceral examinations (including fetal body weight, dimensions, and extensive cardiac evaluations), skeletal examinations (Alizarin Red-stained specimens), and organ weights.

Pre- and Postnatal Developmental Study

Pregnant cynomolgus monkeys (20/group) received daclizumab once weekly at 0 or 50 mg/kg from GD50 until parturition (~GD160 \pm 10). For 6 months postpartum/postnatal (lactation period), adult females and infants were evaluated for changes in clinical signs, body weight, hematology, lymphocyte phenotyping evaluation [fluorescence-activated cell sorting (FACS) analysis], toxicokinetics, ADAs, and/or serum immunoglobulin analyses. Infants were evaluated for developmental parameters, including neurobehavioral and external assessments, morphometric measurements, and functional assessment of immune system [T cell-dependent antibody response (TDAR) challenge]. Infants were euthanized on birth day 180 \pm 1 (weaning) and external and visceral examinations were conducted, including macroscopic and microscopic tissue examinations.

All institutional and national guidelines for the care and use of laboratory animals were followed.

Clinical

Pregnancy outcomes from adults with relapsing MS who received at least one dose of daclizumab in the phase II SELECT study [10], phase III DECIDE study [11], and ongoing phase III immunogenicity OBSERVE study, or their respective extension studies [for SELECT: SELECTION [9], SELECTED [12, 13]; for DECIDE: EXTEND (NCT01797965)] were included in this analysis.

All study designs were approved by institutional review boards and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and its amendments. Informed consent was obtained from all individual participants included in the studies.

During the controlled studies, clinic visits occurred every 4 weeks for daclizumab administration and safety and tolerability assessments; during the extension studies, visits were every 4–12 weeks. Patients who discontinued treatment were encouraged to remain in the studies and complete follow-up assessments as scheduled, with ≥ 6 months of safety follow-up.

Females who were considering becoming pregnant or who were currently pregnant or breastfeeding were excluded from daclizumab clinical studies. Male and female patients of childbearing potential were required to practice effective contraception and to continue contraception for 4 months after their last dose of study treatment. If a woman became pregnant during any study, immediate discontinuation of study treatment was required. Investigators were required to report pregnancies and the subsequent outcome. Patients were considered to be exposed to daclizumab from the time of the first dose of

daclizumab until 180 days (6 months) after their last dose of daclizumab.

RESULTS

Nonclinical

A summary of reproductive and developmental toxicity studies conducted with daclizumab in cynomolgus monkeys is shown in Table 1.

Male Fertility Study

There were no daclizumab effects on mortality, clinical signs, food consumption, sperm counts, motility or morphology, serum chemistry or hematology parameters, serum testosterone, or organ weights, or any treatment-related histologic findings in the reproductive tract in male animals.

Exposure was confirmed in all treated animals. No ADAs or NABs to daclizumab were detected. The no-observed-adverse-effect level (NOAEL) was the highest dose evaluated (200 mg/kg).

Female Fertility Study

There were no daclizumab-related effects on mortality, clinical condition, food consumption, body weight, clinical chemistry, hematology parameters, estrogen and progesterone levels, or fertility parameters including histopathology. No treatment-related changes in menstrual cycle or ovarian function and no histopathologic changes in the reproductive tract or adrenal and pituitary glands were observed.

Exposure was confirmed in all treated animals. Three animals tested positive for daclizumab ADAs (10-mg/kg group, $n = 2$; 50-mg/kg group, $n = 1$). A strong NAB response in one animal in the 10-mg/kg group

Table 1 Reproductive and developmental toxicity studies conducted with daclizumab in cynomolgus monkeys

Type of study	Duration of dosing	Doses (mg/kg)	NOAEL (mg/kg) ^a	Multiple of human exposure ^a
Male fertility and early embryonic development	9 weeks (~60 days to cover all stages of spermatogenesis)	0	200	102
		10		
		50		
		200		
Female fertility and early embryonic development	9 weeks (~2 menstrual cycles)	0	200	85
		10		
		50		
		200		
Embryo–fetal development	GD20–50 (period of organogenesis)	0	200	140
		10		
		50		
		200		
Pre- and postnatal development	GD50—parturition GD160 ± 10	0	50	55
		50		

GD gestation day, NOAEL (reproductive and developmental toxicity) no-observed-adverse-effect level

^a Based on human exposure (area under curve for days 0–28) in OBSERVE, a pharmacokinetic study of daclizumab in patients with multiple sclerosis [31]

was associated with a significant decrease in serum daclizumab concentration on, and after, day 57; the other ADA-positive animal showed exposure levels similar to all other animals in the group. In the 50-mg/kg group, NAb testing was not performed due to weak transient ADA response and high drug levels. The NOAEL was the highest dose evaluated (200 mg/kg).

Embryo–Fetal Developmental Study

There were no daclizumab-related effects on any of the pregnant animals. Food consumption, body weight, body weight gain, and hematology and serum chemistry parameters were in normal ranges and comparable with control animals.

Of the 53 cynomolgus fetuses, there were a total of six losses across all groups, including controls, with a slightly higher incidence in the 200-mg/kg group. However, the fetal loss was not deemed related to daclizumab, as the combined loss from the pilot (Biogen and AbbVie Biotherapeutics Inc., data on file) and Good Laboratory Practice studies was within the range of spontaneous fetal loss for the test facility, no developmental fetal effects were observed, and a correlation was observed between low maternal body weight and fetal loss, with an uneven distribution of animals with lower maternal body weights distributed to receive 200 mg/kg (Biogen and AbbVie Biotherapeutics Inc., data on file).

All other 47 cynomolgus fetuses (22 males, 25 females) showed normal growth and development in utero. There were no daclizumab-related fetal abnormalities (malformations and/or variations).

Maternal exposure was confirmed in all animals. Average cord blood daclizumab concentrations on $GD100 \pm 2$ were 1.27, 9.23, and 32.97 mcg/mL at dose levels of 10, 50, and 200 mg/kg, respectively, indicating placental transfer. The maternal/fetal daclizumab ratio at cesarean delivery was 0.5, 0.6, and 0.4 for the 10-, 50-, and 200-mg/kg groups, respectively. Four animals dosed with 10 mg/kg daclizumab had NABs, coincident with pronounced drug loss in one animal; the other three NAB-positive animals showed no significant decrease in exposure. These findings did not impact the overall study conclusions. Maternal and developmental NOAEL was the highest dose evaluated (200 mg/kg).

Pre- and Postnatal Developmental Study

Weekly administration of 50 mg/kg daclizumab to pregnant cynomolgus monkeys during gestation was well tolerated; there were no daclizumab-related changes in clinical signs, food consumption, body weight, clinical pathology (hematology), or serum immunoglobulins during gestation through 6 months postpartum in female cynomolgus monkeys. Effects on gestational duration or pregnancy/postpartum outcomes (i.e., combined fetal and infant losses) were considered unrelated to maternal administration of daclizumab.

Combined fetal and infant losses were comparable between the controls (30%) and daclizumab-treated (40%) animals and were within the historical range for the testing facility (10%–43%). There were three fetal losses in the control group and one in the daclizumab group, all occurring in the third trimester.

A total of 17 control and 19 daclizumab-exposed cynomolgus infants were delivered by natural birth. There were ten infant losses ≤ 29 days postnatally (control group, $n = 3$; daclizumab group, $n = 7$). In four cases (control group, $n = 1$; daclizumab group, $n = 3$), the cause of death was clearly related to lack of maternal care. In five cases (control group, $n = 2$; daclizumab group, $n = 3$), the infants were either delivered prematurely or preterm, had injuries at delivery, or had survival issues due to the mother's poor health. One infant was euthanized due to a fractured femur.

There were no daclizumab-related changes in the fetuses/infants in any of the parameters measured including clinical signs, body weight, morphometric measurements, external assessments, neurobehavioral evaluations, clinical pathology (hematology), lymphocyte phenotyping evaluation (FACS), serum immunoglobulins, or TDAR.

No treatment-related effects were observed in the available placenta or umbilical cord, or in body weights, morphometric measurements, external or gross/visceral evaluations, or histopathology of the brain of aborted or stillborn cynomolgus fetuses (control group, $n = 3$; daclizumab group, $n = 1$), infants that were euthanized or died before the scheduled necropsy (control group, $n = 3$; daclizumab group, $n = 7$), or in the remaining infants that survived to scheduled necropsy on birth day 180 ± 1 .

The mean ratio between daclizumab serum concentrations in the cynomolgus infant and corresponding mother 14 days after birth was approximately one. Daclizumab was detected in both the milk and serum of 9/19 animals 2 weeks after parturition; concentrations in milk were $\leq 0.122\%$ of that found in the serum of the same animal.

ADA samples were not analyzed, as decreased exposure indicating ADAs was not detected. As there were no daclizumab-related maternal or developmental effects through 6 months postpartum, NOAEL was determined to be 50 mg/kg.

Clinical Pregnancy Outcomes

A total of 2236 patients had received at least one dose of daclizumab across the clinical study program and, as of November 14, 2014, there were 5213.6 patient-years of exposure. As of March 9, 2015, 45 pregnancies in 40 patients were reported with daclizumab; pregnancy outcomes are shown in Table 2. There were 38 pregnancies in 36 women that occurred during daclizumab exposure (on treatment or ≤ 6 months from the last dose) and six pregnancies in five women that occurred off daclizumab treatment (> 6 months after the last dose).

In total, four women became pregnant more than once: two were during daclizumab exposure and then again > 6 months after their final dose of daclizumab and were counted in both groups.

Among the 38 daclizumab-exposed pregnancies, there were 20 live births, four spontaneous abortions or miscarriages (11%), eight elective terminations, and two ectopic pregnancies. In patients with live births, the mean number of doses before pregnancy was 13.3 (range 1–44), and in patients with spontaneous abortions the mean number of doses before pregnancy was 9.83 (range 2–21). Two pregnancies were lost to follow-up and the outcome for two is pending. A congenital abnormality occurred in one live birth in daclizumab-exposed pregnancies (see “[Live Births](#)”). There were three live births, two spontaneous abortions, and one elective

termination in women who were off daclizumab treatment at conception.

Live Births

Among live births from daclizumab-exposed pregnancies (i.e., during treatment or ≤ 6 months after last dose, $n = 20$), 18 were full term (≥ 36 weeks' gestation), one woman gave birth to twins via elective cesarean delivery at 32 weeks because of the twin pregnancy, and gestational age at birth was unknown in one woman. Maternal ages at conception ranged from 22 to 38 years.

One congenital abnormality [heart defect: complex transposition of great vessels (TGV)] was observed in one live birth; the infant was born to a woman who had received six doses of daclizumab, but discontinued treatment < 4 months before conception and had been receiving IM interferon beta-1a for 1 month at the start of the pregnancy. She also had been receiving lisinopril. Surgery was performed on the infant to correct the complex TGV. The investigator considered this congenital defect unrelated to daclizumab.

Among live births from pregnancies that occurred off daclizumab treatment (i.e., > 6 months after last dose; $n = 3$), two were full term (each delivered at 38 weeks). One was delivered prematurely due to maternal history of pre-eclampsia; the infant was healthy. Maternal ages at conception ranged from 32 to 34 years.

Spontaneous Abortions

There were six spontaneous abortions in the daclizumab clinical study program: four occurred in pregnancies exposed to daclizumab. At conception, the women's ages ranged from 26 to 33 years. Gestational ages at the time of their final dose ranged from ~ 2 to 4 weeks, and gestational ages at the time of

Table 2 Pregnancy outcomes in the daclizumab clinical study program

Pregnancies by outcome ^a	Became pregnant while receiving daclizumab or ≤6 months after the final dose	Stopped daclizumab treatment >6 months before becoming pregnant	Daclizumab dose status unknown at the time of becoming pregnant
Total number of pregnancies	38	6	1
Total number of women who became pregnant ^b	36 ^c	5 ^d	1
Live birth	20	3	0
Spontaneous abortion/ miscarriage	4	2	0
Elective termination	8	1	0
Ectopic pregnancy	2	0	0
Lost to follow-up	2	0	0
Outcome pending	2	0	1

^a Based on pregnancy reports from the daclizumab drug development program as of March 9, 2015

^b Four women became pregnant more than once; two of these women became pregnant while receiving daclizumab or ≤6 months of receiving the final dose and then again >6 months after their final dose of daclizumab and are therefore counted in both columns

^c Of the 36 women who became pregnant while receiving daclizumab or ≤6 months of receiving the final dose, 34 had one pregnancy (total pregnancies, $n = 34$) and two had two pregnancies in this category (total pregnancies, $n = 4$)

^d In the five women who became pregnant >6 months after their final dose of daclizumab, four had one pregnancy each (total pregnancies, $n = 4$) and one had multiple ($n = 2$) pregnancies in this category

spontaneous abortion ranged from 5 to 9 weeks. Two of the four women had predisposing risk factors (prior miscarriages and tobacco use) for miscarriage [15]. In women who had been off daclizumab treatment for >6 months at conception, there were two spontaneous abortions. Gestational ages at the time of spontaneous abortion were ~4 and ~10 weeks; one of these women had had a prior pregnancy during treatment with daclizumab with an outcome of live birth.

Elective Terminations

Of the elective terminations reported in the program, eight occurred in women exposed to

daclizumab at conception and one in a woman who had been off daclizumab for >6 months. One patient underwent an elective termination because of a high risk of perinatal complications and the procedure was performed without problem. No fetal defects were reported.

Ectopic Pregnancies

Ectopic pregnancies occurred in two women (31 and 32 years of age when they became pregnant) during daclizumab exposure. In one patient, the gestational age at the time of the last daclizumab dose was 10 weeks. In the other patient, the ectopic pregnancy began 3 months after the last dose. The gestational ages at the

time the pregnancies were terminated were ~8 and ~10 weeks. One of these women had a history of miscarriage and had previously had a spontaneous abortion (see “[Spontaneous Abortions](#)”) during the study at ~2 months before the ectopic pregnancy; she conceived again at a later point in the study, >6 months after the last dose, and gave birth to a healthy infant. Formal medical details were not available for the second ectopic pregnancy, which was reported by the patient.

DISCUSSION

The reproductive and developmental toxicity for daclizumab has been thoroughly evaluated for effects on fertility, embryo–fetal development, and pre- and postnatal development and growth. In nonclinical studies in cynomolgus monkeys, biweekly (once every other week) daclizumab had no effects on surrogate male or female fertility end points at doses up to 200 mg/kg (highest dose tested; exposure in females and males up to 85-fold and 100-fold higher than the clinical dose, respectively). Once-weekly daclizumab at doses up to 200 mg/kg in pregnant female cynomolgus monkeys between GD20 and 50 (period of organogenesis) had no discernible maternal or embryo–fetal effects. The 200-mg/kg daclizumab dose corresponds to 140-fold exposure at the efficacious 150-mg clinical dose.

In the pre- and postnatal study, once-weekly administration of 50 mg/kg daclizumab from GD50 until parturition in pregnant cynomolgus monkeys was well tolerated. There were no daclizumab-related maternal or developmental effects through 6 months postpartum. The frequency and nature of fetal and infant losses that occurred were within the range of normal variation for developmental and reproductive

toxicology studies at the testing facility and within expected outcomes for live birth studies of this type in cynomolgus monkeys [16]. Several infant losses were secondary to maternal neglect, which is a background finding in primigravid cynomolgus monkeys [17]. The 50-mg/kg daclizumab dose provided a 55-fold safety margin over the clinical dose of 150 mg.

Across the daclizumab clinical study program, 45 pregnancies have been reported, 38 of which occurred during daclizumab exposure. Among pregnancies exposed to daclizumab with known outcomes, 20/38 were live births, 4/38 spontaneous abortions, 8/38 elective terminations, and 2/38 ectopic pregnancies. The spontaneous abortions occurred early in pregnancy (≤ 10 weeks' gestation) and the incidence in women exposed to daclizumab (11%) was consistent with the early pregnancy loss rate (12%–26%) in the general population [15]. Two women who conceived while receiving daclizumab were lost to follow-up; outcomes are pending for two pregnancies that occurred in women exposed to daclizumab and one pregnancy for which the timing of the last daclizumab dose is unknown.

Daclizumab exposure did not appear to be associated with a higher risk of preterm births [5% (1/20) of daclizumab-exposed pregnancies], which was comparable with the rate reported in the general population (5%–10%) [18]. No patterns of specific birth defects were observed, with one congenital abnormality of complex TGV reported in the fetus of a woman who stopped daclizumab treatment <4 months before becoming pregnant and was receiving IM interferon beta-1a for 1 month, concomitant with lisinopril, at conception; this event was not considered by the investigator to be treatment related.

The estimated half-life of daclizumab is 21–25 days and is characterized by slow

clearance [19]; therefore, there is potential for fetal exposure when pregnancy begins ≤ 6 months of the last dose. In terms of pharmacodynamics, that daclizumab may affect uterine CD56^{bright} NK cells also should be considered; however, the expansion of the phenotypically different peripheral CD56^{bright} cells was reversible following 24 weeks of treatment discontinuation [9]. Thus, exposure risk should be considered in women receiving daclizumab and who wish to conceive.

Pregnancy outcomes have been reported from post-marketing surveillance, prospective observational studies, and analyses of clinical trial databases for SC interferon beta-1a [20], IM interferon beta-1a [21], interferon beta-1b [22], glatiramer acetate [23], natalizumab [24, 25], fingolimod [26], teriflunomide [27], delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) [28], alemtuzumab [29], and the chemotherapeutic agent mitoxantrone [30]. Overall, data regarding the effects of interferon beta and glatiramer acetate on fertility, pregnancy, and lactation are relatively reassuring [1, 30]. Animal studies have indicated that natalizumab administration may result in reduced fertility, with no human studies published to date [1, 30]. The most recent data from the natalizumab pregnancy registry do not suggest any effect of exposure on pregnancy outcomes [25]; nevertheless, except for severely active cases, natalizumab should not be used before conception [30]. While fingolimod does not appear to negatively impact fertility, cases of abnormal fetal development, coupled with a teratogenic effect in animals, mean that avoiding its use in pregnancy is strongly recommended [1, 30]. Teriflunomide does not affect the overall fertility in animal studies, despite reducing sperm counts in rats [30]. Results from a retrospective analysis global

pharmacovigilance database do not indicate a teratogenic signal nor other adverse pregnancy outcomes [27]. Nevertheless, based on nonclinical leflunomide data, teriflunomide has a black box warning for teratogenicity and is therefore contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception [30]. Some regulatory authorities also have recommended that men wishing to father a child should discontinue teriflunomide and undergo the accelerated elimination procedure due to its presence in human semen at low levels [27]. Delayed-release DMF did not appear to impair fertility or exert teratogenic effects in animals; data from clinical trials and post-marketing databases do not suggest an increased risk of fetal abnormalities or adverse pregnancy outcomes with gestational exposure [28]. Fertility and pregnancy outcome data are limited for alemtuzumab; animal studies indicate possible reproductive toxicity, while exposure during the clinical trial program does not suggest a teratogenic risk [29, 30]. Mitoxantrone has shown embryotoxicity in animal and human studies; therefore, pregnancy should be excluded before each infusion [30]. Overall, treatment benefits for the mother (or father) must be balanced against potential risks to the fetus when deciding how to manage planned pregnancies.

CONCLUSION

In summary, animal studies showed no effects of daclizumab on maternal well-being, embryo–fetal development, fertility, and pre- and postnatal development and growth. The numbers of pregnancies in the daclizumab clinical study program are small and therefore do not allow definitive conclusions. In addition,

patients enrolled in clinical studies may not be wholly representative of the overall population of individuals with MS. However, data on pregnancies in women exposed to daclizumab during the clinical study program do not suggest an increased risk of adverse pregnancy outcomes with regard to the fetus or mother. Data from any further pregnancies occurring during the ongoing extension studies and in post-marketing experience will continue to be collected.

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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