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Pregnancy Data from the BG-12 (Dimethyl Fumarate) Development Program

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INTRODUCTION

- Oral BG-12 (dimethyl fumarate) is approved in the United States for the treatment of relapsing forms of MS.
- Experimental evidence shows that BG-12 may have anti-inflammatory and cytoprotective/anti-oxidative activity via the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway.[1,2]
- In the Phase 3 DEFINE and CONFIRM studies, BG-12 demonstrated significant clinical and neuroradiologic efficacy over 2 years with an acceptable safety profile in patients with relapsing–remitting MS.[3,4]
- As MS is most common in women of childbearing age, it is important to evaluate the effects of BG-12 exposure on pregnancy.
  - Reproductive toxicology of dimethyl fumarate has been investigated in rats and rabbits.
  - No formal studies of BG-12 have been conducted in pregnant women, but pregnancies have occurred during the BG-12 clinical development program.

OBJECTIVE

- To present results from animal reproductive toxicology studies and pregnancy outcomes reported during the BG-12 clinical development program.

METHODS

Animal Reproductive Toxicology Studies

- Reproductive and developmental toxicology was evaluated in rats and rabbits given dimethyl fumarate during organogenesis or during pregnancy and lactation (Table 1).
  - The effects of dimethyl fumarate on male and female fertility were evaluated in rats.
- Dimethyl fumarate aqueous suspension was administered by oral gavage.

Table 1: Dimethyl fumarate animal reproductive toxicity studies

Study	Species (number per group)	Dimethyl fumarate doses (mg/kg)	Duration
Developmental and reproductive	Sprague Dawley rats (25 pregnant females + 3[a] or 6[b] for toxicokinetic analysis)	0, 25, 100, 250	12 days (GD7 to GD18)
Developmental and reproductive	New Zealand white rabbits (20 pregnant females + 3[b] for toxicokinetic analysis)	0, 25, 75, 150	14 days (GD7 to GD20)
Peri- and postnatal development	Sprague Dawley rats (25 pregnant females; 25 male and 25 female pups)	0, 25, 100, 250	Adults: 35 days (from GD7 to LD21) Pups observed through to sexual maturity
Male fertility	Sprague Dawley rats (25 males, 25 untreated females)	0, 75, 250, 375	≥70 days during cohabitation
Female fertility	Sprague Dawley rats (25 females, 25 untreated males)	0, 25, 100, 250	21 days prior to cohabitation and up to GD7

[a]In the control group; [b]In the dimethyl fumarate-dosed groups.
GD = gestation day; LD = lactation day.

- Clinical observations, body weight, weight changes, food consumption, and necropsy observations were evaluated in adults and pups (where relevant) in all studies.
  - Additional assessments for the individual studies are summarized in Table 2.

Table 2: Study-specific assessments of animal reproductive toxicity

Study	Study-specific assessments
Developmental and reproductive studies	Adult: general appearance, toxicokinetics, pregnancy status Fetus: body weight, sex, alterations (external, soft tissue, skeletal)
Peri- and postnatal development	Adult: number/distribution of implantation sites, viability, postpartum toxicokinetics, maternal behavior, litter observations, natural delivery Pup: viability, toxicokinetics, post-weaning development (passive avoidance testing, sexual maturation, watermaze testing, reproductive capacity), number/distribution of corpora lutea, implantation sites, uterine contents, selected male organ weights; fetal body weight, sex, gross external alterations
Male fertility	Estrous cycle, mating and mating performance, Caesarean section parameters, sperm evaluation, organ weights, histopathology (kidneys, pancreas, stomach, epididymis, prostate and seminal vesicles)
Female fertility	Viability, estrous cycling, mating, toxicokinetics, number/distribution of corpora lutea, implantation sites, uterine contents

Clinical Monitoring Procedure for Pregnancy

- In the BG-12 clinical trial program:
  - Women considering becoming pregnant while in the study or who were pregnant and lactating were excluded
  - Male and female subjects of childbearing potential were required to use effective contraception
  - All women who became pregnant were required to discontinue treatment immediately.

Clinical Analysis of Pregnancy

- All pregnancies occurring during BG-12 clinical trials and their outcomes were recorded (data cut-off: January 2, 2013).
- The population analyzed included 2,665 patients with MS, 320 patients with psoriasis, 101 rheumatoid arthritis patients, and 338 healthy volunteers.

RESULTS

Animal Reproductive Toxicology Studies

- There was no evidence of fetal teratogenicity with dimethyl fumarate treatment in developmental and reproductive studies.
  - In female rats, reduced body weight gain and food consumption were accompanied by decreased fetal weight and increases in fetal alterations (reduced ossification) at the highest dose (250 mg/kg) which is approximately 10-fold the human therapeutic dose based on area under the curve. The fetal effects were considered secondary to maternal toxicity from intolerability to the dimethyl fumarate suspension and were not expected to affect offspring growth or survival.
  - In rabbits, reduced maternal body weight gain and increased abortion were observed at dimethyl fumarate doses approximately equivalent to 7 and 16 times the 240 mg twice-daily human dose, respectively.
  - Fetal effects were seen only at maternally toxic doses of dimethyl fumarate and are therefore unlikely to represent a risk to humans.
- Consistent with other preclinical studies, maternal reductions in body weight and weight gain were seen with high-dose dimethyl fumarate in the peri- and postnatal rat study.
  - Offspring body weight was significantly reduced at the highest dimethyl fumarate dose, followed by significantly delayed preputial separation (both sexes) and sexual maturation (females).
  - Dimethyl fumarate had no effects on learning, short- or long-term retention, response inhibition (assessed by performance on a passive avoidance test), or mating and fertility parameters in offspring.
- There was no evidence that dimethyl fumarate impaired fertility in male or female rats.
  - In males, minimal/mild interstitial cell hyperplasia in the testis was observed with all doses but had no effect on fertility.
  - In females, reductions in body weight, body weight gain, and food consumption were observed at the highest dose but with no consequent effects on fertility.

Clinical Pregnancy Outcomes

- As of January 2, 2013, 56 pregnancies were reported in BG-12 clinical studies: 38 in subjects exposed to BG-12 (37 MS patients, 1 healthy volunteer), 14 in placebo-treated subjects, and 4 in subjects exposed to glatiramer acetate (GA).
- Outcomes are known for 34 of 38 pregnancies in subjects who received BG-12, for all pregnancies in subjects who received placebo, and for 3 of 4 pregnancies in subjects who received GA (Table 3).

Table 3: Pregnancy outcomes by treatment group

Pregnancy outcome	Placebo	BG-12	GA	Total
Live birth	9	22[a]	1	32
Spontaneous abortion	3	3[b]	0	6
Elective termination	2	9	2	13
Information pending	0	3	0	3
Total no. of women who became pregnant[c]	14	38	4	56

Data cut-off: January 2, 2013.
[a]Two subjects had discontinued BG-12 for >60 days at the time of their last menstrual period; [b]One subject had discontinued BG-12 240 mg three times daily (TID) 4 months earlier and was taking interferon beta-1a prior to the spontaneous abortion; [c]One subject in each of the BG-12 and GA groups was lost to follow-up.

- Similar proportions of pregnancies in BG-12- and placebo-treated subjects resulted in live births (65% and 64%, respectively; Table 3).
  - No fetal abnormalities were reported for any of the live births.
  - Of the 22 live births in subjects receiving BG-12, 20 were full term (>37 weeks gestation) and 2 were premature (35 weeks gestation). Both premature births occurred in subjects who had not received BG-12 for approximately 60 days at the time of their last menstrual period.
- Spontaneous abortions occurred in 3 pregnancies (9%) in BG-12-treated subjects and 3 pregnancies (21%) in subjects receiving placebo (Table 3).
  - These spontaneous abortions occurred early during the first trimester (≤12 weeks gestation).
  - The incidence of spontaneous abortion was consistent with the expected rate of early pregnancy loss in the general population (12–22%).[5]
  - One spontaneous abortion occurred in a subject exposed to BG-12 TID at the time of conception and was considered possibly related to BG-12 by the investigator.
  - One spontaneous abortion occurred in a subject who had discontinued BG-12 TID approximately 4 months previously and then received interferon beta-1a as rescue therapy until an estimated gestational age of 6 weeks. This event was considered unrelated to BG-12 by the investigator.

CONCLUSIONS

- Animal studies showed no evidence of impaired fertility or teratogenicity with dimethyl fumarate at doses that cause reductions in maternal weight gain.
- There is no clinical evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes associated with gestational exposure to BG-12 during the first trimester, although data are limited.
- Further data on the impact of BG-12 treatment during pregnancy will be collected through a Phase 4 pregnancy registry.

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