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Fetal Exposure with Ponesimod Treatment Across Clinical Development Studies

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BACKGROUND

- Multiple sclerosis (MS) is 3 times more common in women than in men and typically diagnosed between the ages of 20-50, a time of childbearing potential.[1]
- There is limited data for the class of sphingosine 1-phosphate (S1P) receptor modulators in pregnant women.[2,3]
- Based on animal studies, adverse effects on embryofetal development and teratogenicity have been noted with S1P receptor modulators.[2,3]
- Women of childbearing potential should therefore use effective contraception to avoid pregnancy during treatment with S1P receptor modulators and for a period of time following discontinuation (based on the respective half-life and clearance periods).[2]

INTRODUCTION

- Clinical studies of ponesimod excluded pregnant women and breastfeeding women.
- Women of child-bearing potential who enrolled in clinical studies of ponesimod were to use protocol-defined acceptable methods of contraception and were not to become pregnant during study treatment and for at least 1 month after study drug discontinuation.
- Pregnancy tests were performed prior to study entry, regularly during study treatment, as well as 1 month after study drug discontinuation.
- We report the outcomes of pregnancies that occurred in the ponesimod clinical development program, despite clinical study protocols requiring a negative pregnancy test at enrollment and use of reliable contraception by women of childbearing potential in all studies.

OBJECTIVE

- The primary objective was to assess the risk of reproductive and embryofetal toxicity in women exposed to ponesimod during pregnancy in the ponesimod clinical development program.

METHODS

- Pregnancy outcomes were evaluated in women exposed to ponesimod during pregnancy across all phase 2 and 3 studies including their long-term safety extensions **(Table 1)**.
- Ponesimod treatment was discontinued if a patient became pregnant.
- Any pregnancy that occurred during the study including 30 days following ponesimod discontinuation was reported.
- Pregnancy cases were followed to its conclusion and outcomes were reported.

Table 1: Distribution of Female Patients Treated with Ponesimod in Phase 2 and 3 Studies

Study	Phase	Patient Population	Female patients (all ages) (n)
AC-058A200	2	Plaque PsO	8
AC-058A201	2	Plaque PsO	63
AC-058C202	2	GVHD	1
AC-058B201/B202	2/LTE	MS	295
AC-058B301/B303	3/LTE	MS	653
AC-058B302	3	MS	42
Total			1062

GVHD, graft-versus-host disease; MS, multiple sclerosis; PsO, psoriasis; LTE, long-term extension

RESULTS

- Across all studies, including 1062 women, 20 pregnancies with fetal exposure to ponesimod, all during the first trimester, were reported as of September 2021 **(Table 2)**.
- Nineteen pregnancies were reported in patients with MS (n=990) (ponesimod 20 mg: n=17; other doses: n=2, one patient each receiving 10 mg and 40 mg as part of a long-term phase 2 dose finding study).
- One pregnancy was reported in a patient who received ponesimod 20 mg as part of a phase 2 study in chronic plaque psoriasis (n=63).
- Of the 20 pregnancies, outcomes were reported in 18 pregnancies: 6 normal newborns, 8 induced abortions (no indication of fetal toxicity: n=5; benign hydatidiform mole: n=1; unknown: n=2), and 4 spontaneous abortions.
- Outcomes were not reported in 2 pregnancies (pregnancy ongoing: n=1; lost to follow up: n=1) (**Table 2**).
- Among cases of abortion (n=12), the presence of fetal abnormalities were reported as unknown in 11 cases (one remaining case: benign hydatidiform mole).
- All pregnancy cases were assessed by the investigator as not related to study treatment, except for 1 case of benign hydatidiform mole and 1 case of spontaneous abortion.

Table 2: Pregnancies with Fetal Exposure to Ponesimod

Pt ID	Study / Pt population	Age at time of pregnancy*	Ponesimod dose at time of pregnancy (mg)	Action taken with ponesimod	Outcome	Reason for induced abortion	Related to study treatment?
1	Ph 2 LTE - MS	28	10	Withdrawn	Induced abortion	NR	No
2	Ph 3 LTE - MS	41	20	Withdrawn	Induced abortion	Not medical (desire to continue in study)	No
3	Ph 3 - MS	30	20	Withdrawn	Induced abortion	Not medical (patient concern for potential fetal anomaly without medical substantiation)	No
4	Ph 3 - MS	21	20	Withdrawn	Induced abortion	Not medical (did not desire a child)	No
5	Ph 2 LTE - MS	32	40	Withdrawn	Induced abortion	Unknown	No
6	Ph 2 LTE - MS	32	20	Withdrawn	Induced abortion	Molar pregnancy	Yes
7	Ph 3 LTE - MS	39	20	Withdrawn	Induced abortion	Not medical (patient concern for potential fetal anomaly without medical substantiation)	No
8	Ph 3 LTE - MS	47	20	Withdrawn	Induced abortion	Not medical (desire to continue in study)	No
9	Ph 2 LTE - MS	41	20	Withdrawn	Spontaneous abortion	NA	No
10	Ph 2 - Plaque PsO	31	20	NA	Spontaneous abortion	NA	No
11	Ph 3 LTE - MS	40	20	Withdrawn	Spontaneous abortion	NA	Yes
12	Ph 3 LTE - MS	29	20	Withdrawn	Spontaneous abortion	NA	No
13	Ph 2 LTE - MS	29	20	Withdrawn	Normal newborn	NA	No
14	Ph 2 LTE - MS	30	20	Withdrawn	Normal newborn	NA	No
15	Ph 3 - MS	27	20	Withdrawn	Normal newborn	NA	No
16	Ph 3 - MS	29	20	Withdrawn	Normal newborn	NA	No
17	Ph 3 LTE - MS	34	20	Withdrawn	Normal newborn	NA	No
18	Ph 3 LTE - MS	31	20	Withdrawn	Normal newborn	NA	No
19	Ph 3 LTE - MS	25	20	Withdrawn	Lost to follow-up	NA	No
20	Ph 3 LTE - MS	33	20	Withdrawn	Ongoing	NA	No

*As reported in adverse event form
ID, identification; MS, multiple sclerosis; NA, not applicable; NR, not reported; Ph, Phase; LTE, long-term extension; PsO, psoriasis; Pt, patient

CONCLUSIONS

- **The proportion of spontaneous abortions in patients with MS (3/19, 15.8%) was within range of that reported for the general population (14.2%-20.9%)[4,5] and within the range reported for the unexposed MS population (4.3%-21.1%).[6,7]**
- **Based on the limited clinical data available to date, there is no indication of reproductive embryofetal toxicity with ponesimod treatment.**
- **Women of childbearing potential should use effective contraception to avoid pregnancy during ponesimod treatment and for 1 week after discontinuation.[8,9]**
- **Recognizing the importance of collecting more information on pregnancy exposure, a multinational Pregnancy Outcomes Enhanced Monitoring program (POEM) has been established in order to record prospective data through enhanced pharmacovigilance monitoring of cases of women exposed to ponesimod during pregnancy reported to the Janssen global safety database from post-marketing reports and reports from the ponesimod clinical trials program.[10]**

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Disclosures:
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