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Cumulative Pregnancy and Infant Outcomes in Patients With Multiple Sclerosis Following Maternal Exposure to Ofatumumab: Results From the Novartis Safety Database

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KEY FINDINGS & CONCLUSIONS

- As of September 25, 2023, a total of 279 prospectively identified pregnancies in women exposed to ofatumumab, with 55 known pregnancy outcomes resulting in 57 foetuses/infants (two pregnancies involving twins), were reported in the Novartis Global Safety Database
- No major congenital anomalies or serious infections were reported in the 29 prospective live births
- Given the limited data, conclusions cannot be made on the generalisability of the current observations
- Novartis will continue to collect information on outcomes from women exposed to ofatumumab during pregnancy

- A prospective, observational registry on maternal and infant outcomes in women exposed to ofatumumab during pregnancy is currently active in the United States/Canada and Germany (NCT05634967):
  - OTIS/MotherToBaby (US and Canada): Please call 1-877-311-8972 or visit https://mothertobaby.org/join-study/
  - DMSKW (Germany): Please visit https://www.ms-und-kinderwunsch.de

INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for the treatment of relapsing multiple sclerosis in adults[1,2]
- The FDA and EMA labels of ofatumumab both state that women of childbearing potential should use effective contraception during treatment with ofatumumab and for 6 months after the last dose[1,2]
- Clinical data on the effect of ofatumumab treatment on pregnancy outcomes are currently limited
- Based on current knowledge,
  - Transient B-cell depletion and lymphopenia have been observed in infants whose mothers were exposed to other anti-CD20 antibodies during pregnancy[3,4]
  - The maternal-foetal transfer of immunoglobulin G (IgG) during the first trimester is minimal and foetal IgG concentration starts to rise from the second trimester[5,6]
  - Exposure to ofatumumab during gestation did not cause maternal toxicity in cynomolgus monkeys, and no adverse effects were observed on prenatal or postnatal development[7]

OBJECTIVE

- To report the latest cumulative pregnancy and infant outcomes data in women treated with ofatumumab during or in the 6 months prior to pregnancy

METHODS

- The Novartis Global Safety Database includes cases from clinical trials and the post-marketing setting collected via the non-interventional **PR**egnancy outcomes **I**ntensive **M**onitoring (PRIM) study
- Data on spontaneously reported pregnancies are collected using a set of targeted and structured checklists
- Pregnancy outcomes were analysed in women exposed to ofatumumab during pregnancy or up to 6 months prior to their last menstrual period (LMP) (cutoff date: September 25, 2023)
- Pregnancy and infant outcomes were collected from the reporting of pregnancy up to a maximum of 1 year of the infant's age (**Figure 1**)
- This analysis was focused on outcomes in prospective cases with maternal exposure during pregnancy. Outcomes in retrospective cases are provided separately for completeness and are expected to be subject to an inherent reporting bias toward abnormal outcomes due to the retrospective nature
- **Prospective cases** are defined as cases for which, at the time of initial reporting (i.e. first receipt by Novartis), the pregnancy outcome has not yet occurred or there is no report of an abnormal prenatal testing result (including cases where prenatal testing has not yet been performed or cases where prenatal testing has been performed but results were either not received yet by provider, normal, or not specified)
- **Retrospective cases** are defined as cases for which, at the time of initial reporting (i.e. first receipt by Novartis), the pregnancy outcome has already occurred or prenatal testing results were abnormal (regardless of whether the pregnancy outcome has occurred)
- PRIM is a non-interventional study, and no information on B-cell depletion or immunoglobulin/haematological abnormalities is expected to be collected as part of this study

Figure 1. Pregnancy and foetal/infant outcomes

Pregnancy outcomes
- Live births
- Stillbirths
- Induced terminations[a]
- Abortion NOS
- Spontaneous abortions
- Ectopic pregnancies

Foetal/infant outcomes
- Congenital malformation (major/minor/NOS/chromosomal anomalies)
- Infections requiring hospitalisation
- Vaccination reaction
- Developmental delays

[a]Includes therapeutic and elective terminations.
NOS, not otherwise specified.

RESULTS

PROSPECTIVE CASES

Patient characteristics and exposure to ofatumumab

- As of September 25, 2023, 279 prospective pregnancies with maternal exposure to ofatumumab were identified
- Pregnancy cases by reporting type are summarised in **Figure 2** and maternal demographics in **Table 1**

Figure 2. Pregnancy cases by reporting type

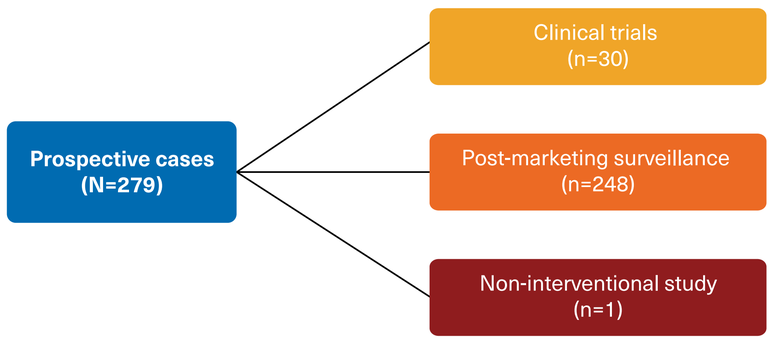


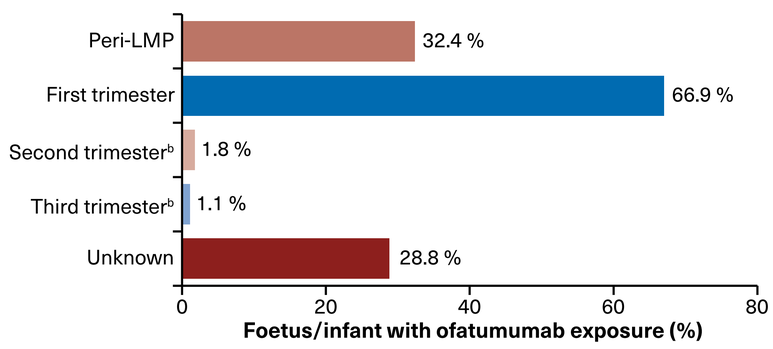
Table 1. Maternal demographics

Demographics	
Maternal age at LMP (years), n (%)	161 (57.7)
– Mean (SD)	31.4 (5.89)
– Min, Max	18, 44
Region – n (%)	279 (100)
– North America	149 (53.4)
– Western Europe	47 (16.8)
– Asia and Oceania	44 (15.8)
– Other	39 (14.0)
Gestational age at reporting (weeks), n (%)	93 (33.3)
– Median	~7

LMP, last menstrual period; SD, standard deviation.

- Most foetuses/infants (n=188; 66.9%) were exposed to ofatumumab during the first trimester; for 81 patients (28.8%), the exact timing of exposure was unknown (**Figure 3**)

Figure 3. Exposure to ofatumumab (foetal/infant cohort[a]; N=281)



[a]The 279 prospective pregnancy cases included a cohort of 281 foetuses/infants (two pregnancies involving twins). Some pregnancies involved more than one trimester of exposure to ofatumumab and therefore are included in more than one category in the figure above. The peri-LMP period for ofatumumab refers to the 180 days prior to the LMP. [b]Cases exposed to ofatumumab in the second and third trimester either resulted in normal live births, or include pending outcomes or were lost to follow-up. LMP, last menstrual period.

Pregnancy and infant outcomes

- As of September 25, 2023, among 279 prospective cases, there were 55 known pregnancy outcomes, 123 cases were ongoing at data lock point and 101 cases were lost to follow-up
- Outcomes consisted of 29 live births, 12 induced terminations, 4 ectopic pregnancies, 11 spontaneous abortions and 1 abortion (not otherwise specified) (**Figure 4**; **Table 2**)

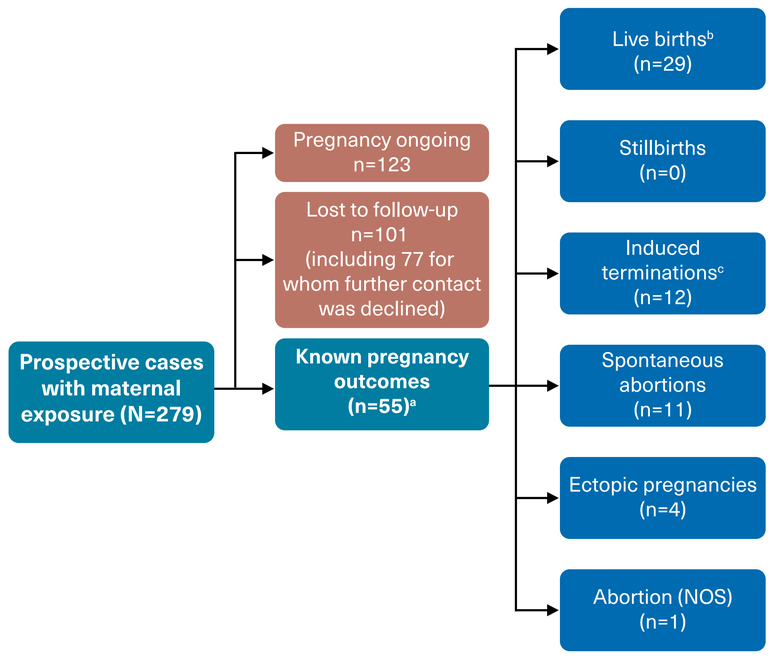
Table 2. Pregnancy outcomes by trimester of exposure (foetus cohort with maternal exposure during pregnancy)

	Live birth[a]	Induced termination[b]	Spontaneous abortion	Ectopic pregnancy	Abortion NOS	Total
Peri-LMP only	3	1	0	0	0	**4**
At least first trimester	20	10	10	2	1	**43**
Peri-LMP or first trimester	23	11	10	2	1	**47**
Overall[c]	29	12	11	4	1	**57**

[a]Includes one case of minor congenital malformation (hydronephrosis) and one set of twins. [b]Includes therapeutic and elective terminations with another set of twins. [c]Includes unknown trimester and other combinations of trimester.
LMP, last menstrual period; NOS, not otherwise specified.

- In the 29 prospective live births, there were
  - 28 full-term newborns including one set of twins
  - One premature newborn (34 weeks of gestation)
  - No major congenital anomalies or serious infections

Figure 4. Pregnancy outcomes in prospective cases



[a]Two pregnancies involving twins. [b]Includes newborn with a minor congenital malformation (hydronephrosis) and one set of twins. [c]Includes therapeutic and elective terminations with another set of twins; one case of trisomy 18 and no reported abnormalities or reason for termination provided in the remaining 11 outcomes.
NOS, not otherwise specified.

RETROSPECTIVE CASES

- As of September 25, 2023, 30 retrospective pregnancy cases were reported in women with MS who were exposed to ofatumumab. One patient discontinued therapy with ofatumumab due to delivery; no further details were provided
- Outcomes in the remaining 29 cases included 9 live births, 3 induced terminations, 16 spontaneous abortions and 1 ectopic pregnancy
- No congenital anomalies were reported

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Abbreviations

CD, cluster of differentiation; **EMA**, European Medicines Agency; **FDA**, Food and Drug Administration; **IgG**, immunoglobulin G; **LMP**, last menstrual period; **MS**, multiple sclerosis; **NOS**, not otherwise specified; **PRIM**, PRegnancy outcomes Intensive Monitoring; **SD,** standard deviation.

Disclosures

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