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Pregnancy and Infant Outcomes in Women With Relapsing Multiple Sclerosis Following Exposure to Ofatumumab: Update From the PRIM Study

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KEY FINDINGS & CONCLUSIONS

- As of September 25, 2024, 669 prospective pregnancy cases were identifiedin the Novartis Global Safety Database in women with MS treated withofatumumab during pregnancy or up to 180 days prior to LMP
- These included 275 cases with initial reporting to Novartis before September25, 2023, i.e., these cases had sufficient time for both short- and long-term pregnancy outcomes to occur
- In the majority of cases, ofatumumab was administered at least during the firsttrimester
- With the increasing number of pregnancy cases, findings suggest that theprevalence estimates of pregnancy outcomes are in line with the backgroundrates observed in the general population and data from MS populations inpharmacovigilance systems
- One major congenital anomaly, falling under "congenital heart defects", themost common EUROCAT organ system, was reported in a full-term live birth
- Ongoing data collection will continue to increase the precision of these estimates
- A prospective, observational registry on maternal and infant outcomes inwomen exposed to ofatumumab during pregnancy is currently active in theUS/Canada and German-speaking countries (NCT05634967):
  – OTIS/MotherToBaby (US and Canada): Please call1-877-311-8972 or visithttps://mothertobaby.org/join-study/
  – DMSKW (Germany and German-speaking countries): Please visithttps://www.ms-und-kinderwunsch.de

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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 (MS) in adults[1,2]
- The United States (US) Food and Drug Administration and European Medicines Agency labels of ofatumumabboth state that women of childbearing potential should use effective contraception during treatment withofatumumab and for 6 months after the last dose.[1,2] However, pregnancies may occur during this interval
- Based on current knowledge:
  – In humans, maternal–fetal immunoglobulin G transport across the placenta is an active process mediated by theneonatal Fc receptor, which increases progressively only from the early second trimester and is almostnon-existent in the first trimester[3–5]
  – Exposure to ofatumumab during gestation did not cause maternal toxicity in cynomolgus monkeys, and noadverse effects were observed on prenatal or postnatal development[6]

OBJECTIVE

- To report the cumulative pregnancy and infant outcomes data in women with MS treated with ofatumumab duringpregnancy or up to 180 days prior to last menstrual period (LMP)

METHODS

- The Novartis Global Safety Database includes cases from clinical trials and the post-marketing setting (spontaneous reports,patient support programs, etc., and excluding registry cases) collected via the non-interventional **PR**egnancy outcomes Intensive **M**onitoring (PRIM) program
- Data on spontaneously reported pregnancies are collected using a set of targeted and structured checklists up to a maximum of1 year of the infant's age
- For this ofatumumab PRIM study analysis:
  – Pregnancy and infant outcomes in women with MS administered ofatumumab during pregnancy or up to 180 days prior to theirLMP reported before September 25, 2024, are included
  – The focus is mainly on prospective cases* with maternal ofatumumab administration during pregnancy
  – To account for detection bias towards early pregnancy outcomes, the prevalence for pregnancy outcomes is estimated in casesreported prior to September 25, 2023, allowing sufficient time for both short- (e.g., early termination, spontaneous abortion) andlong-term (e.g., live birth, still birth) outcomes to occur
  – Cases of malformation are reviewed by an independent adjudication panel and classified per EUROCAT guidelines
- Based on ofatumumab administration, cases are classified as:
  – **Peri-LMP only**: If the case is reported with administration only during the peri-LMP period (from 180 days before LMP to LMP)
  – **At least 1st trimester**: If the case is reported with at least one administration in the 1st trimester irrespective of administration inperi-LMP or after 1st trimester
  – **Only after 1st trimester**: If the case is reported with administration only after the 1st trimester (no or unknown administrationnoted for peri-LMP or 1st trimester)
- The ofatumumab PRIM study is a non-interventional study, and no information on B-cell depletion or immunoglobulin/hematological abnormalities is expected to be collected as part of this study
- Pregnancy and fetal/infant outcomes are shown in **Figure 1**
- ***Prospective cases definition**: At the time of initial reporting to Novartis, the pregnancy outcome has not occurred or there isno report of an abnormal prenatal test result (i.e., no prenatal testing was performed or prenatal testing was performed and the results were not received by the reporter, normal, or not specified)

Figure 1. Pregnancy and fetal/infant outcomes

Pregnancy outcomes
- Live birth
- Stillbirth (no sign of life at or after 22 weeks of complete gestation)
- Induced termination*
- Abortion NOS
- Spontaneous abortion (no sign of life prior to 22 weeks of gestation)
- Ectopic pregnancy

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

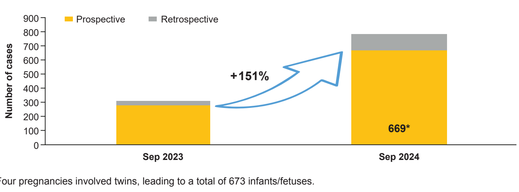
*Alncludes therapeutic and elective terminations.
NOS, not otherwise specified.

RESULTS

Case accumulation and maternal characteristics

- As of September 25, 2024, 669 prospective and 107 retrospective pregnancies in women with MS administered ofatumumabwere identified (**Figure 2**). Four prospective pregnancies involved twins, leading to a total of 673 infants/fetuses
- Maternal demographics in prospective cases are shown in Table 1

Figure 2. Accumulation of pregnancy cases over time



*Four pregnancies involved twins, leading to a total of 673 infants/fetuses.

Table 1. Maternal demographics in prospective cases

Demographics	Cumulative cases – initial reporting before September 2024; N=669
Maternal age at LMP (years)	
n (%)	398 (59.5)
Median	31.0
Q1, Q3	28, 35
Region	
n (%)	669 (100)
High-income North America	326 (48.7)
Western Europe	173 (25.9)
Asia and Oceania	74 (11.1)
Other	96 (14.3)
Gestational age at reporting (weeks)	
n (%)	212 (31.7)
Median	8

LMP, last menstrual period; n (%), number (%) of pregnancies with non-missing information among N; Q, quartile.

Ofatumumab administration

- Among the 275 prospective cases reported prior to September 25, 2023, exposure information was available for 221 cases.Ofatumumab was last administered within 180 days before the LMP in 12% of cases, while in 0.5% of cases, ofatumumab wasadministered only after the 1st trimester. In the remaining 87% of cases, ofatumumab was administered at least during the1st trimester (Figure 3)

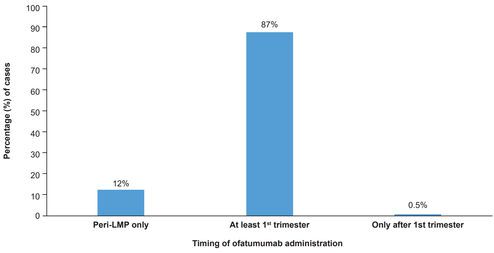
Pregnancy and infant outcomes

Table 2. Pregnancy outcome (fetus/infant cohort)

Initial reporting	Cases with at least 1-year follow-up – initial reporting before September 2023 (controlling for detection bias)			Cumulative cases – initial reporting before September 2024 (subject to detection bias)		
Exposure based on last ofatumumab administration	Total[c]	Only peri-LMP	At least 1st trimester	Total[c]	Only peri-LMP	At least 1st trimester
Number of pregnancies[a]	N=275	N=27	N=193	N=673*	N=82	N=395
Known outcome	n=103	n=9	n=87	n=156	n=15	n=120
Live births[a]	**73 (70.9%)**	**6**	**62**	**98**	10	79
Full-term[a]	*47 (64.4%)*	*3*	*40*	*59*	*4*	*50*
Pre-term[a]	*7 (9.6%)*	*1*	*6*	*9*	*1*	*8*
Post-mature[a]	*1 (1.4%)*	*0*	*1*	*1*	*0*	*1*
Unknown gestational timing	*18 (24.7%)*	*2*	*15*	*29*	*5*	*20*
Ectopic pregnancy[a]	**2 (1.9%)**	0	2	**5**	1	3
Induced termination[a,e,f]	**13 (12.6%)**	2	10	**16**	2	12
Abortion NOS[a]	**1 (1.0%)**	0	1	**1**	0	1
Intrauterine/fetal death						
Stillbirth[a]	**1 (1.0%)**	0	1	**1**	0	1
Spontaneous abortion[a,g]	**13 (12.6%)**	1	11	**35**	2	24
Congenital malformation in live birth/still birth/TOPFA						
Major	**0**	0	0	**1**	0	1
Minor	**2**	0	2	**2**	0	2
Chromosomal/genetic	**1**	0	1	**2**	0	1

[a]Percentage among number of cases with known outcome. [b]Percentage among total live births. [c]Total includes cases with unknown timing of administration and administration only after 1st trimester. [d]Based on further case evaluation, one induced termination will be corrected, post-extraction, to spontaneous abortion. [e]Includes lost to follow-up (n=284) and ongoing pregnancies with pending outcome (n=233). [f]Induced termination includes cases of therapeutic abortion and elective termination. [g]Spontaneous abortion includes cases of hydatidiform mole and blighted ovum.
LMP, last menstrual period; NOS, not otherwise specified; TOPFA, termination of pregnancy for fetal anomaly.

Figure 3. Ofatumumab administration (cases with initial reporting prior to September 2023, fetal/infant cohort with exposure information, n=221)



- Among the 275 prospective cases reported prior to September 25, 2023, 103 cases had known pregnancy outcome and included73 (70.9%) live births, 13 (12.6%) induced termination (including 1 termination due to chromosomal anomaly), 13 (12.6%)spontaneous abortions, 1 (1.0%) abortion NOS, 1 stillbirth, and 2 (1.9%) ectopic pregnancies (**Table 2**)
  – The prevalence of spontaneous abortions is consistent with that expected in the general population[7–9] and in the overall MSpopulation[10]
- Two infants (from full-term live birth) were adjudicated with minor congenital anomalies that resolved without intervention: one caseof hemangioma (<1 cm in the scalp) and one case of hydronephrosis
- Since September 2023, one infant was adjudicated as having major congenital malformation leading to a prevalence of1.14% (n=1/N LB+SB+TOPFA with known fetal outcome=88, 95% CI [0.03% – 6.17%]). This was a case of truncus arteriosuspersistent, classified as "congenital heart defect" reported in a full-term live birth–
  " Congenital heart defect" is the most frequently observed organ system per EUROCAT with a background prevalence of 0.69 per100 cases
- In the 1st year of life, neonatal infections were reported in two infants and neurodevelopmental delay and movement disorder(due to prematurity) in one infant

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Abbreviations
CD, cluster of differentiation; **CI**, confidence interval; **EUROCAT**, European Registration of Congenital Anomalies and Twins; **LB**, live birth; **LMP**, last menstrual period; **MS**, multiple sclerosis; NOS, not otherwise specified; PRIM, PRegnancy outcomes Intensive Monitoring; **Q**, quartile; **SB**, still birth; **TOPFA**, termination of pregnancy for fetal anomaly; **US**, United States.

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