Pregnancy Outcomes in Patients With MS Following Exposure to Ofatumumab: Updated Results From the Novartis Safety Database

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Background and objective

Background

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for the treatment of RMS in adults[1,2]
- The FDA and EMA labels of ofatumumab both state that women of childbearing potential should use effective contraception during the 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-fetal transfer of IgG during the first trimester is minimal and fetal IgG concentration starts to rise from the second trimester[5]
    - Exposure to ofatumumab during gestation did not cause maternal toxicity in cynomolgus monkeys, and no adverse effects were observed on prenatal or postnatal development[6]

Objective

To report the latest cumulative pregnancy outcome data in women with MS exposed to ofatumumab during, or in the 6 months prior to, pregnancy

CD, cluster of differentiation; EMA, European Medicine Agency; FDA, Food and Drug Administration; IgG, Immunoglobulin G; MS, multiple sclerosis; RMS, relapsing MS.

1.Kesimpta (ofatumumab). Prescribing Information. Accessed February 6, 2023. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf; 2. Kesimpta (ofatumumab). Summary of product characteristics. Accessed February 6, 2023. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf; 3. Chakravarty EF, et al. *Blood* 2011;117:1499-1506; 4. Das G, et al. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e453; 5. Pentsuk N, van der Laan JW. *Birth Defects Res B Dev Reprod Toxicol*. 2009;86(4):328-344; 6. Bellot M, et al. *Reprod Toxicol*. 2022 Mar;108:28-34.

Methods

- The Novartis Global Safety Database (pharmacovigilance system) 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 in women with MS exposed to ofatumumab during pregnancy or 6 months prior to their last menstrual period (LMP) were analyzed (cutoff date: September 25, 2022)
  - Pregnancy and infant outcomes were collected from the reporting of pregnancy up to a maximum of 1 year of infant's age
  - The focus of the analysis included outcomes in **prospective cases**. Outcomes in retrospective cases are provided separately for completeness and are subject to reporting bias

Prospective and retrospective cases

- **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 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)

Maternal and infant outcomes

Pregnancy outcomes

- Live births
- Stillbirths
- Induced terminations[a]
- Spontaneous abortions[b]
- Ectopic pregnancy

Infant outcomes

- Congenital malformation (major/minor/NOS)
- Infections requiring hospitalization
- Vaccination reaction
- Developmental delays

[a]Includes therapeutic and elective terminations. [b]Includes spontaneous abortions and abortion not specified.
NOS, not otherwise specified.

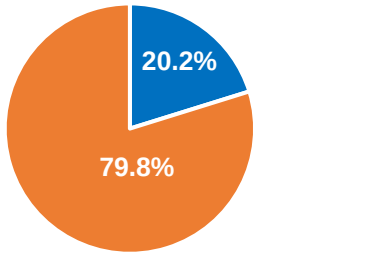
Baseline characteristics and exposure to ofatumumab
Prospective cases

- As of September 25, 2022, 104 prospective pregnancies with maternal exposure to ofatumumab were identified
- Among **prospective cases**, most of the women were exposed to ofatumumab in the first trimester

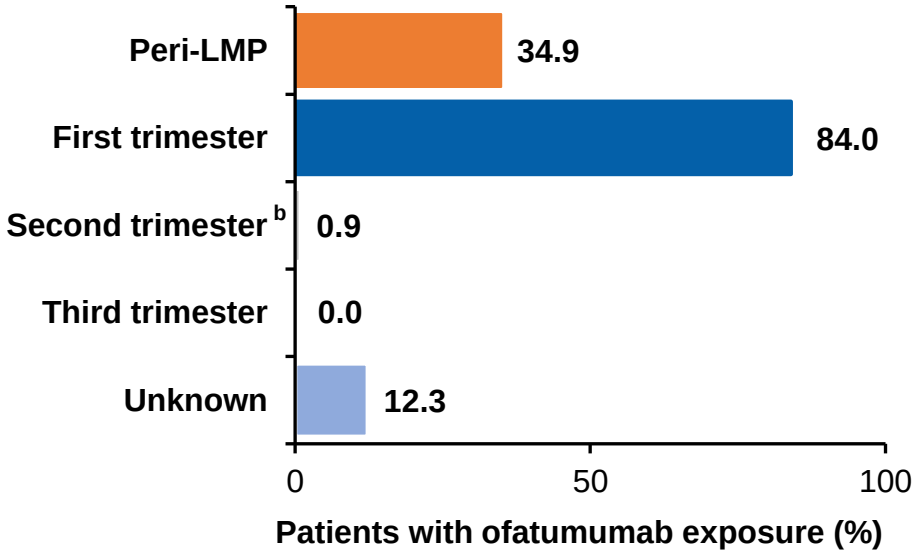
Baseline characteristics

Age, median (range) n=74	Gestational age at reporting, median n=46
32.0 (18–47) years	**~6.8** weeks

Pregnancy cases by reporting type



Exposure to ofatumumab in prospective cases (Fetal cohort; N=106)[a]

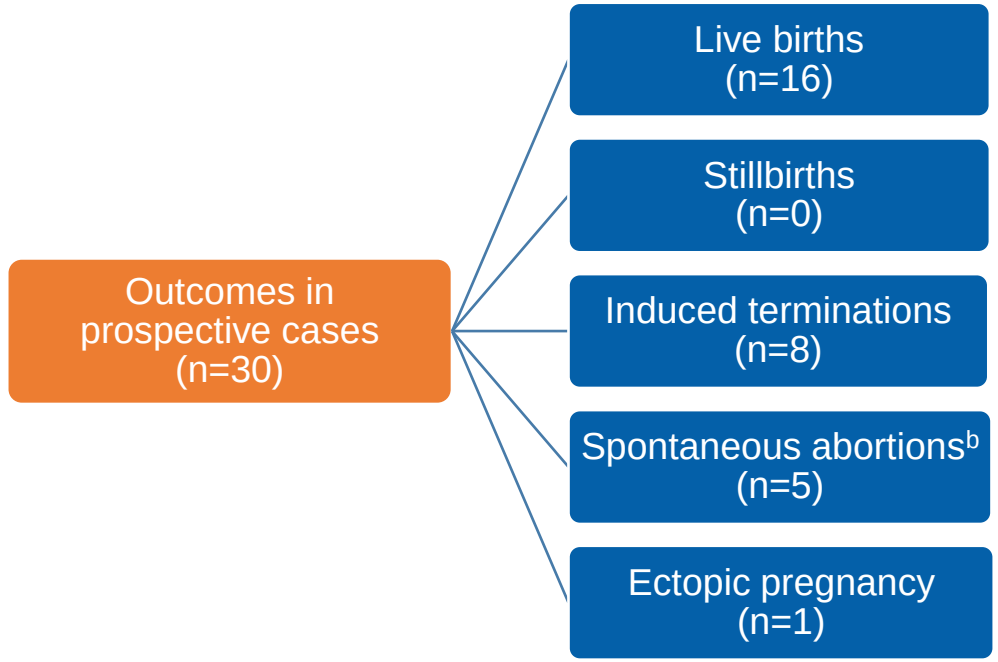


[a]104 prospective cases include cohort of 106 fetuses (two pregnancies involving twins). Peri-LMP period for ofatumumab refers to 180 days prior to the LMP. [b]1 case was lost to follow-up.
LMP, last menstrual period; n, pregnancy cases with available data.

Pregnancy outcomes
Prospective cases

- As of the cut-off date, 30 outcomes were known in 104 prospective cases[a]
- No congenital anomalies were reported in the 16 live births

Pregnancy outcomes in prospective cases (n=30)



[a]In the cohort of 106 fetuses (two pregnancies involving twins), 30 pregnancy outcomes were lost to follow-up (including outcome missing) and 46 pregnancy outcomes were pending.
[b]Includes one blighted ovum and one abortion NOS. All spontaneous abortion were reported in first trimester.
NOS, not otherwise specified.

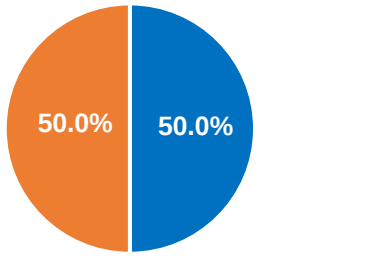
Baseline characteristics and exposure to ofatumumab
Retrospective cases

- As of September 25, 2022, 14 retrospective pregnancies were reported in women with MS who were exposed to ofatumumab
- Among **retrospective** cases, most of the women were exposed to ofatumumab either in the peri-LMP period or in the first trimester

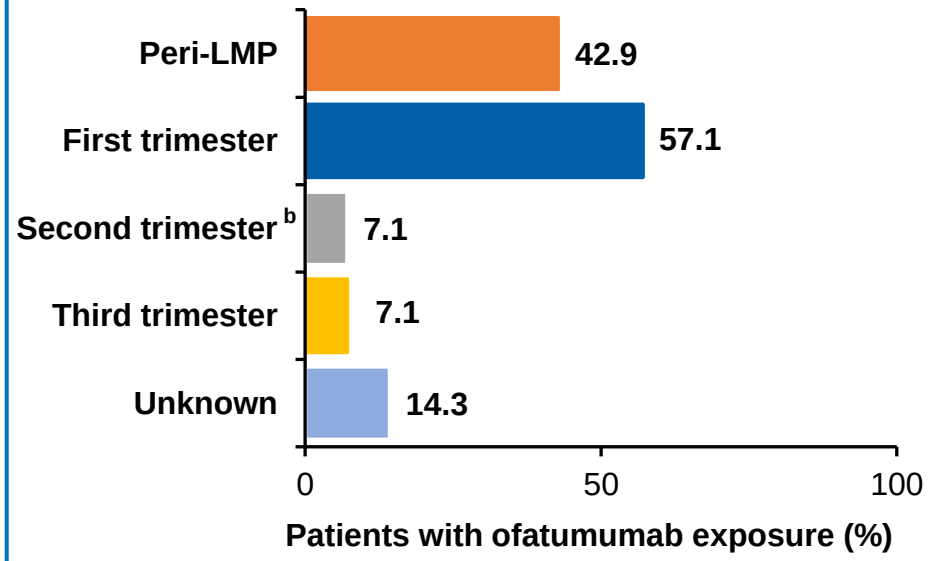
Baseline characteristics

Age, median (range) n=10	Gestational age at reporting, median n=7
32.0 (26–43) years	**~10.4** weeks

Pregnancy cases by reporting type



Exposure to ofatumumab in retrospective cases (Fetal cohort; N=14)[a]

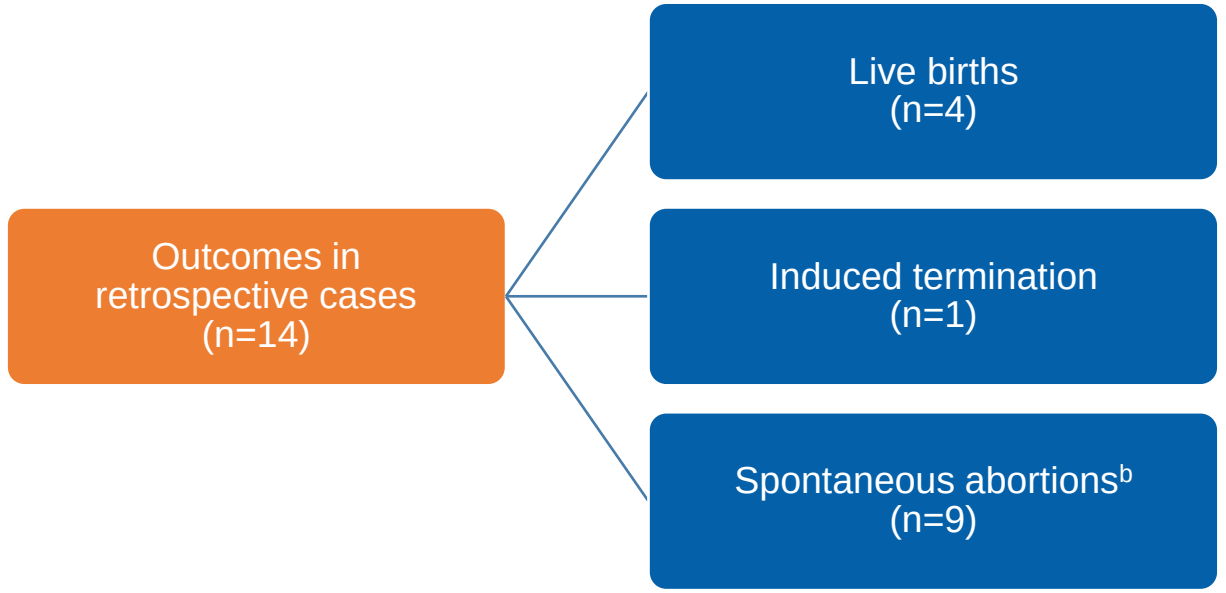


[a]14 retrospective cases include cohort of 14 fetuses. Peri-LMP period for ofatumumab refers to 180 days prior to the LMP. [b]1 case was with live birth.
LMP, last menstrual period; n, pregnancy cases with available data.

Pregnancy outcomes
Retrospective cases

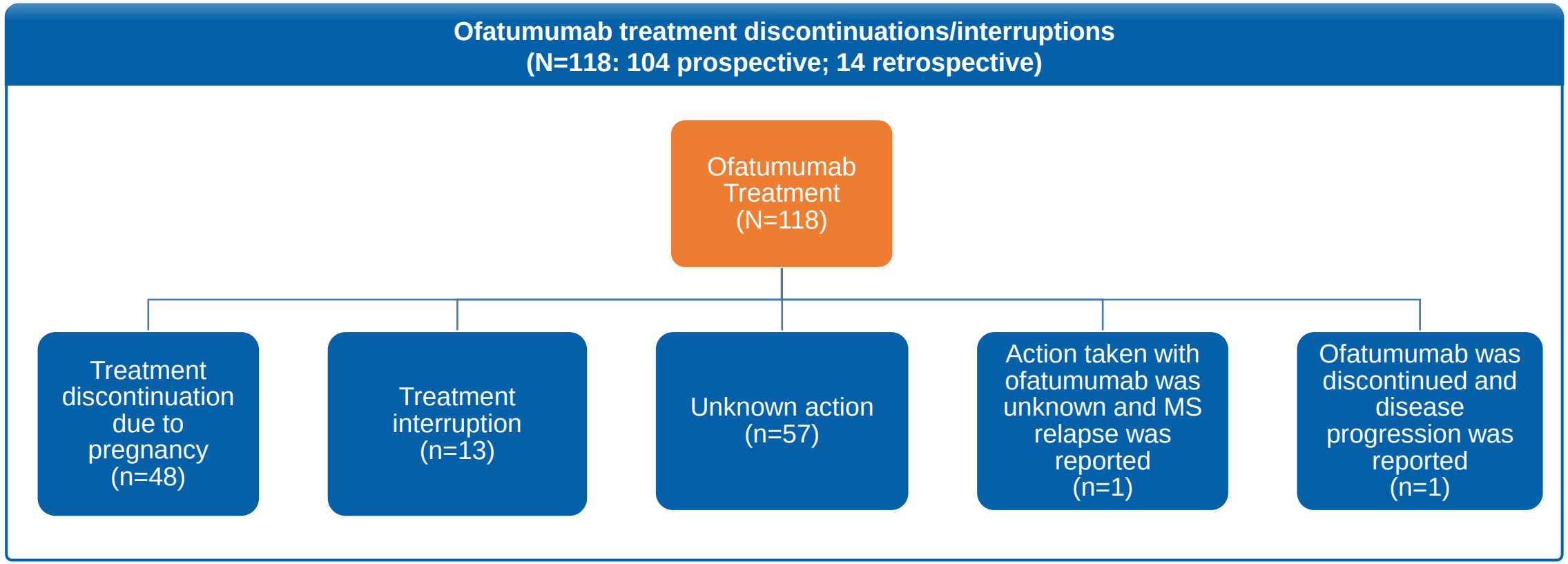
- As of the cut-off date,14 outcomes were reported in 14 retrospective cases[a]
- No congenital anomalies were reported in the 4 live births
- Cases reported retrospectively have an inherent reporting bias toward abnormal outcomes

Pregnancy outcomes in retrospective cases (n=14)



[a]In the cohort of 14 fetuses, no pregnancy outcomes were lost to follow-up (including outcome missing) and none of the pregnancy outcomes were pending.
[b]Includes one blighted ovum and one abortion NOS.
NOS, not otherwise specified.

Ofatumumab treatment discontinuations/interruptions



MS, multiple sclerosis.

Infant outcomes in women with RMS exposed to ofatumumab

- In the 16 live births reported prospectively:
  - No congenital anomalies
  - No serious infections
- PRIM is a non-interventional study, and no information was available on B-cell depletion or immunoglobulin/hematological abnormalities at the time of this analysis

PRIM, **PR**egnancy outcomes **I**ntensive **M**onitoring (PRIM) study; RMS, relapsing multiple sclerosis.

Conclusions

- From the Novartis Safety Database with the current data cutoff (September 25, 2022), a total of 104 prospectively identified pregnancies in women with RMS exposed to ofatumumab were reported, with 30 known outcomes
- A total of 14 cases were reported retrospectively and outcomes were known in all cases by the cut-off date
- The limited number of cases retrieved so far, in conjunction with the number of pregnancies with a pending outcome, does not yet allow for conclusion on the generalizability of the observations made so far
- No congenital anomalies or serious infections were reported in the live births
- 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/

RMS, relapsing multiple sclerosis.