Pregnancy Outcomes in Patients Treated With Ocrelizumab

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INTRODUCTION AND PURPOSE

- Ocrelizumab (OCR), a humanised monoclonal antibody that selectively targets CD20+ B cells, is approved for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS)[1,2]
  - A total of 4,611 patients have received OCR in clinical trials (as of 7 January 2019)
  - Approximately 93,572 patients have received OCR in the post-marketing setting (as of 31 March 2019)
  - Estimated patient exposures from clinical trials and the post-marketing setting are 14,329[a] and 80,276[b] patient years, respectively
- A significant proportion of patients eligible for treatment with OCR will be women of reproductive age
  - Mean age of RMS onset is approximately 30 years[3]
  - Female-to-male ratio of patients with RMS is approximately 3:1[3]
- Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and embryo–foetal development[1]

For a summary of pre-clinical data, please scan here

- Studies on the effect of OCR on human reproduction and neonatal B-cell levels following maternal exposure have not been performed
- Transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20+ antibodies during pregnancy
- A previously reported overview[4] of pregnancy outcomes in OCR clinical trials across indications (RMS, PPMS, rheumatoid arthritis and systemic lupus erythematosus ; (dose range, 20–2,000 mg) concluded that women of childbearing potential should use contraception while receiving OCR and for the period of time recommended by local labelling after the last infusion[1,2] (rationale described in **Box 1**)

[a]Clinical trial database cut-off, 7th January 2019; [b]Model-based estimate using drug dispensary information (non-USA) and claims databases (USA) from 31st March 2019.

Box 1. Rationale for use of contraception during and after OCR treatment

- Effective contraception should be used while receiving OCR and for the period of time recommended by regional labelling[a] after the last infusion of OCR to provide for interpatient drug-elimination variability[1,2]
- Interpatient drug-elimination variability:
  - First-order elimination processes are near-complete (>95%) after five half-lives
  - Average $t_{1/2}$ of OCR in patients with RMS is approximately **26 days**[1,2]
  - Near-complete elimination[b] in patients with RMS with an average $t_{1/2}$ is approximately **19 weeks / 4.5 months**
  - Near-complete elimination[b] in a patient with the longest $t_{1/2}$ seen in female patients with RMS (53 days[c]) is approximately **38 weeks / 9 months**
- IgG1 antibodies, such as OCR, do **not** cross the placenta during the first trimester of pregnancy (3 months)[d]
- OCR transfer is assumed to occur only after the 16th week of gestation, and therefore the foetus is protected from exposure during organogenesis[6,7]

[a]Recommendations for the duration of effective contraception may vary for different health authorities; [b]Based on first-order elimination being near-complete (>95%) after 5 half-lives.
IgG1, immunoglobulin G1; OCR, ocrelizumab; RMS, relapsing multiple sclerosis; $t_{1/2}$, terminal half-life.

OBJECTIVE

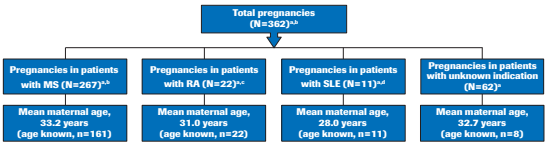
- To report pregnancy, foetal, neonatal and infant outcomes in female patients who became pregnant or who were breastfeeding during OCR trials and post-marketing analyses in multiple sclerosis (MS) up to 31 March 2019

RESULTS

Overall Patient Exposure

- As of 31 March 2019, 362 pregnancies exposed to OCR have been reported (**Figure 1**)

Figure 1. Overview of cumulative maternal exposure pregnancies



[a]N refers to number of pregnancies, not number of women; [b]A further 10 patients received IFN β-1a or placebo during pivotal trials and are excluded from these analyses; [c]One patient with RA experienced two consecutive spontaneous abortions; [d]One patient with lupus nephritis had two consecutive pregnancies, each resulting in the birth of a healthy baby at term.
IFN, interferon; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

All Maternal Exposure Pregnancies in Patients With MS

- Outcomes of the 267 maternal exposure pregnancies in patients with MS are shown in **Table 1**
  - Clinical trials, N=78; post-marketing, N=189 (up to 31 March 2019)
- In total, 57 of 62 recorded live births (92%) resulted in a healthy baby

Table 1. Outcomes of maternal exposure pregnancies in patients with MS[a]

	Exposed *in utero* (n=118)	Unexposed *in utero* (n=47)	Unknown *in utero* exposure (n=102)	Total (N=267)
Outcome	**n (%)**	**n (%)**	**n (%)**	**N (%)**
Pregnancy ongoing	36 (31)	17 (36)	33 (32)	86 (32)
Live birth	31 (26)	18 (38)	13 (13)	62 (23)
Healthy baby	27 (23)	17 (36)	13 (13)	57 (21)
Preterm birth[a]	4 (3)	1 (2)	0	5 (2)
Elective termination	17 (14)	4 (9)	4 (4)	25 (9)[b]
Spontaneous abortion	4 (3)	2 (4)	4 (4)	10 (4)[b]
Ectopic pregnancy	1 (1)	1 (2)	1 (1)	3 (1)
Still birth	1 (1)	0	0	1 (<1)
Unknown outcome[c]	28 (24)	5 (11)	47 (46)	80 (30)

[a]Live preterm birth with abnormal finding; [b]No abnormalities reported; [c]Includes lost to follow-up.

- An overview of outcomes of live births to mothers with MS, including births with abnormal outcomes are presented in **Figure 2**

Maternal Exposure Pregnancies in Patients With an Unknown Indication

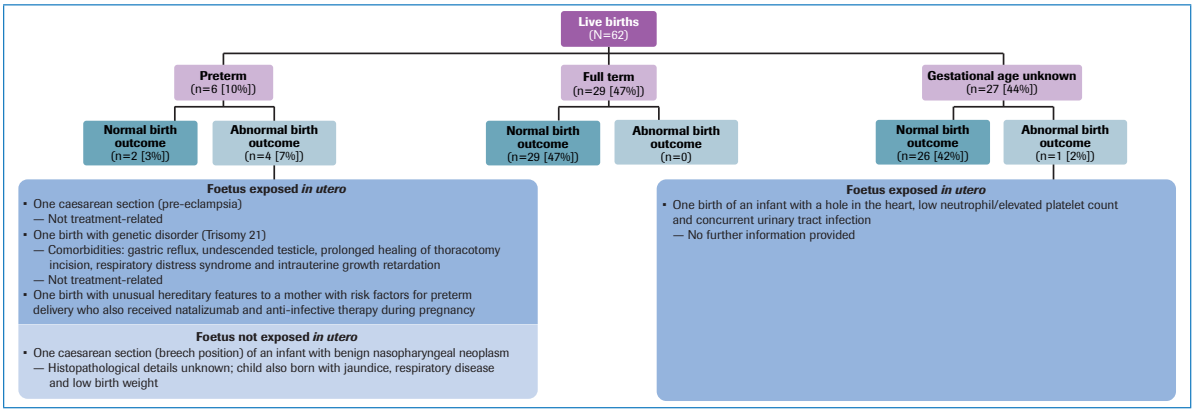
- There were 62 pregnancies in women for which the OCR indication was not reported as of 31 March 2019
  - Eleven pregnancies were ongoing
  - Thirteen pregnancies (12 with foetal exposure) resulted in live births
  - Seven pregnancies resulted in elective terminations (limited data available; six cases may be duplicate cases from Phase III studies)
  - Two pregnancies (both with foetal exposure) resulted in spontaneous abortions
  - Twenty-nine pregnancies had an unknown outcome or were lost to follow-up (foetal exposure *in utero*, n=6; no foetal exposure *in utero*, n=23)

Infant Exposure Through Lactation (as of 31 March 2019)

- There were three cases of infants exposed to OCR via lactation:
  - Two infants were exposed *post partum*; data on maternal exposure, adverse events and infant B-cells were not reported
  - One infant was exposed only *post partum* and had slight B-cell decreases at 1 month of age that were not consistent with true B-cell depletion in terms of level of depletion or rate of return to normal range (1 week)[a]

[a]Mother administered *post partum* OCR for an indication of MS; B-cell decreases not consistent at time of the out-of-range measurement.

Figure 2. Overview of outcomes in live births



Percentages within figure use live births as the denominator.

METHODS

Study Design

- This analysis includes OCR-exposed women with MS recorded from clinical trials and post-marketing experience of OCR
- The database records information from all sources[a] and includes:
  - Clinical trials: all pregnancy cases (including nonserious reports) and all cases with serious adverse events where OCR is considered 'suspect'
  - Spontaneous reports: all cases (serious and nonserious) where OCR is considered 'suspect'
  - Pregnancy outcomes, including information about child health up to 1 year after birth, will be collected in ongoing OCR studies and the OCR pregnancy registry, and post-marketing experience will continue to be collected and assessed
- Prospective and retrospective pregnancy reports were included in this analysis
- Maternal exposure was defined as receiving at least one OCR infusion at any time point before conception and/or during the pregnancy
- An embryo/foetus was considered exposed to OCR *in utero* if the last infusion occurred within 3 months of conception or during pregnancy or if the date of infusion was unknown (see **Box 1**)

[a]Includes clinical trials, noninterventional studies, market research and patient support programmes and spontaneous reports.

CONCLUSIONS

- Reviewed cases are not suggestive of an ocrelizumab-related increased risk of adverse pregnancy / foetal outcomes
  - The current update on pregnancy outcomes remains in line with previous reports
- B-cell levels in neonates following maternal exposure to ocrelizumab have not been studied in clinical trials
  - Transient peripheral B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to other anti-CD20+ antibodies during pregnancy
- Although this report (to 31 March 2019) extends the knowledge base on pregnancy outcomes, the number of pregnancies remain small, limiting the ability to draw conclusions
- Pregnancy and child outcomes (1-year *post partum*) will continue to be collected, including:
  - Ongoing ocrelizumab Phase II, III and IIIb studies and their respective open-label extensions
  - Pregnancy registry (WA40063)[a] and post-marketing experience (BA39732)[a]
- Women of childbearing potential should use contraception while receiving ocrelizumab and for the period of time defined in the local labelling documents after the last infusion of ocrelizumab[1]

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Poster P780