B-Cell Levels and Placental Transfer in Infants Potentially Exposed to Ocrelizumab During Pregnancy: Primary Analysis of the Prospective Multicentre, Open-Label Phase IV MINORE Study

K Hellwig,[1] R Bove,[2] C Oreja-Guevara,[3] R Dobson,[4] E Maillart,[5] D Jacobs,[6] TF McElrath,[7] C Pietrasanta,[8,9] H Kletzl,[10] A Kazlauskaite,[10] D Zecevic,[10] C Raposo,[10] L Craveiro,[10] C-J Lin,[10] N Pasquarelli,[10] S Vukusic[11]

[1]Katholisches Klinikum Bochum, St. Josef Hospital, Universitätsklinikum der Ruhr-Universität, Bochum, Germany; [2]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA; [3]Neurology, Hospital Clínico San Carlos, Idissc, Madrid, Spain; [4]Centre for Preventive Neurology, Wolfson Institute of Population Health, Queen Mary University of London, London, UK; [5]Neurology Department Hôpital de la Pitié Salpêtrière, Assistance Publique des Hôpitaux de Paris, Paris, France; [6]Department of Neurology, Perelman School of Medicine at the Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [7]Division of Maternal-Fetal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [8]NICU, Department of Woman, Child and Neonate, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy; [9]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Service de Neurologie et Sclérose en Plaques, Fondation Eugène Devic EDMUS contre la Sclérose en Plaques, Hôpital Neurologique Pierre Wertheimer, Lyon, France

P087

https://ter.li/j8xfka

See our other pregnancy-related presentations at ECTRIMS: SOPRANINO (O039), pregnancy outcomes (P085) and peripartum disease activity (P591 & P1240)

OBJECTIVE

To measure placental transfer of ocrelizumab from women with MS and evaluate the potential impact on B-cell levels in newborns

KEY TAKEAWAYS

Exposure to **ocrelizumab during pregnancy did not result in infant B-cell depletion**

Ocrelizumab was mostly undetectable in umbilical cord serum at birth and infant serum at Week 6 of life, indicating minimal placental transfer and low exposure of infants to ocrelizumab *in utero*

AEs observed were **typical for pregnancy, delivery, postpartum and infancy**

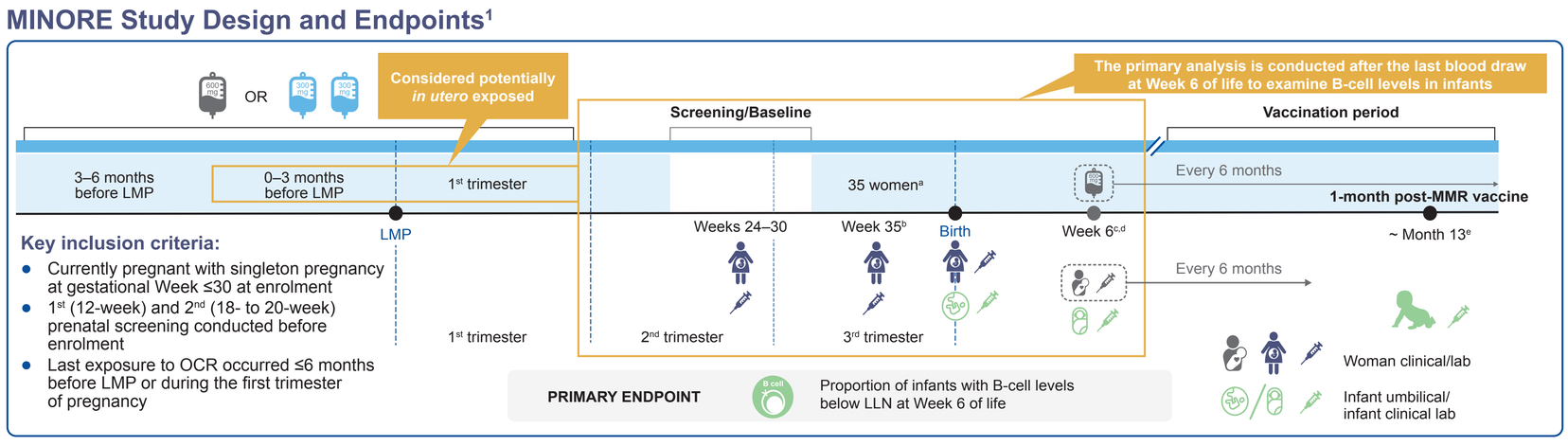
MINORE results indicate that pregnancy is compatible with ocrelizumab treatment and will support clinicians caring for **women with MS who wish to become pregnant** in making evidence-based treatment decisions

INTRODUCTION

- Most DMTs approved for the treatment of MS are not recommended during pregnancy[1]
- Discontinuation of DMTs before pregnancy can increase the risk of maternal disease activity[1]
- Placental transfer of endogenous IgG_1 is known to significantly increase after the first trimester[2]
- It is important to determine the extent of placental transfer of OCR and whether *in utero* exposure to OCR affects B-cell levels in infants[1]
- Here we present the **primary analysis from the MINORE study (NCT04998812)**, the first prospective study to measure placental transfer of OCR from women with MS and the potential impact on B-cell levels in newborns

METHODS

MINORE Study Design and Endpoints[1]



[a]As per the protocol, approximately 33 women were required to be enrolled; [b]± 14 days; [c]± 7 days; [d]Treatment with commercial OCR could be resumed at any time after birth for women who decided not to breastfeed. For those women who decided to resume treatment while breastfeeding, treatment with OCR should have been restarted after collection of the Week 6 infant blood sample if possible; but the decision was left to the discretion of the woman and the investigator. If the woman decided to switch to another DMT postpartum or to stop DMT after birth, no laboratory/clinical assessments were performed for the woman; the infant blood sample at Week 6 of life (± 7 days) was only collected if the woman was not breastfeeding; [e]One month (+ 30 days) after the first/second dose of MMR vaccine, or Month 13 of age (+ 30 days) if the MMR vaccine is not planned to be administered.

RESULTS

MINORE Enrolled 35 Women with RRMS

At screening/baseline	Women (N=35)
Age, years	34 (26–41)
RRMS, n (%)	35 (100)
Duration since MS diagnosis, years	5.4 (1.0–17.0)
EDSS score	1.5 (0.0–4.5)
Gestational age, weeks	26 (22–30)
History of previous pregnancy,[a] n (%)	19 (54.3)
Full-term live birth	15 (78.9)

OCR treatment start[b]: 14.1 months (0.5–50.7)
Last OCR infusion before LMP[c]: 3.2 months (0.3–4.5)
Last OCR infusion after LMP[d]: 1.9 months (0.1–3.2)
1st postpartum OCR infusion[e]: 5.4 weeks (1.9–24.6)
LMP
Birth

Note: displayed values are median (range) unless otherwise stated.
[a]Pre-term live birth (n=1/19), spontaneous abortion (n=1/19), therapeutic abortion (n=1/19), elective abortion (n=1/19), ectopic pregnancy (n=2/19); [b]Overall 7/35 had no other DMT before OCR; [c]A total of 18/35 women received OCR infusions 3–6 months prior to LMP and 14/35 women received OCR infusions 0–3 months prior to LMP; [d]First trimester OCR administration was at 13+4 gestational weeks (n=1), 4 days after LMP (n=1) and 1 month 25 days after LMP (n=1). The woman who received OCR 1 month and 25 days after LMP was lost to follow-up at Week 6; [e]31 women resumed OCR infusions. The first dose was administered as a single 600-mg infusion in 28/31 mothers and as 2x300 mg infusions in 3/31 mothers.
CCOD: 8 April 2024.

All 35 Pregnancies Resulted in Full-Term Live Births, with All Babies Showing Normal Weight, Length and Head Circumference

Head circumference: 35.0 cm (33.0–37.5); 90% within 3rd–97th age percentiles
Weight: 3.4 kg (2.8–4.5); 94.3% within 3rd–97th age percentiles
Length: 51.4 cm (48.0–56.0); 66.7% within 3rd–97th age percentiles[a]

At birth	Infants (N=35)
Delivery, n (%)	
Vaginal	22 (62.9)
Vaginal (forceps/vacuum - instrumental)	4 (11.4)
Caesarean – scheduled	6 (17.1)
Caesarean – emergency	3 (8.6)
Gestational age (weeks)	39 (37–42)
Sex, n (%)	
Male	13 (37.1)
Female	22 (62.9)
Minor congenital anomalies,[b] n (%)	2 (5.7)
Major congenital anomalies,[c] n (%)	1 (2.9)

Note: displayed values are median (range) unless otherwise stated.
[a]All babies were above 3rd percentile; [b]cryptorchism minor CA, persistent foramen ovale minor CA; [c]Hypospadias (unconfirmed) major CA, classified as per EUROCAT Guide 1.5.[3]
CCOD: 8 April 2024.

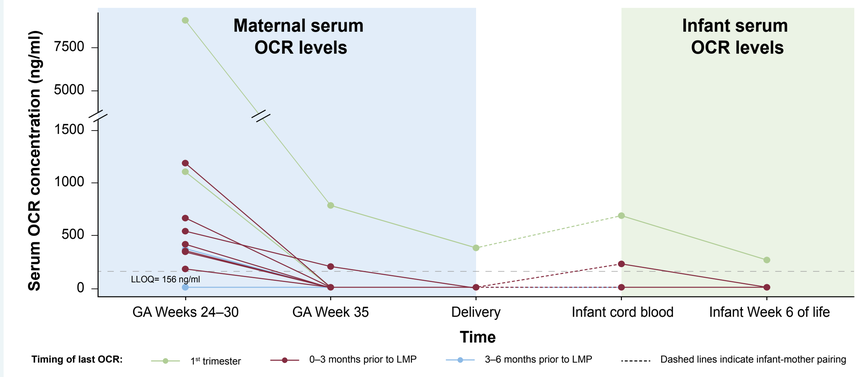
OCR was Mostly Undetectable in Umbilical Cord Samples at Birth and No B-Cell Depletion was Observed at Week 6

Mothers received OCR infusion
n=18 3–6 months, n=14 0–3 months, n=3 1st trimester

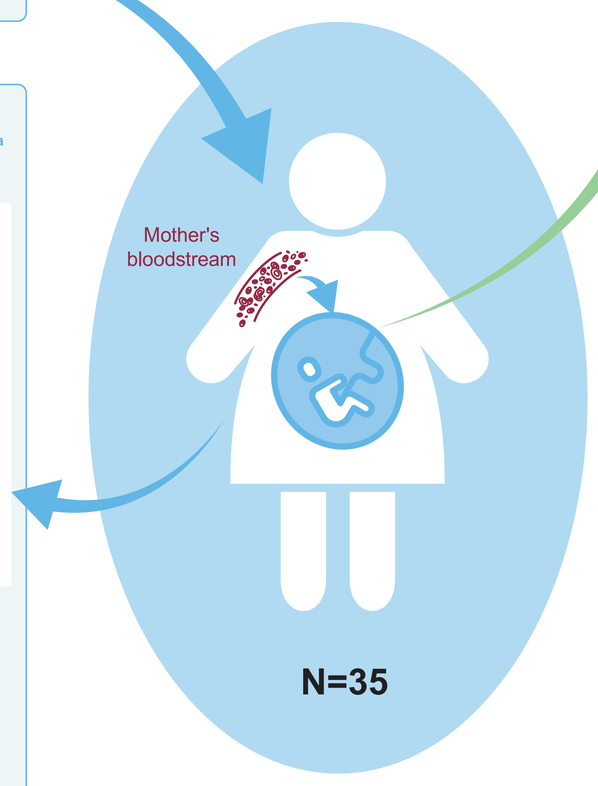
Weeks 24–30
OCR was **undetectable**[a] in 24/35[b] women (68.6%)

Week 35
OCR was **undetectable**[a] in 32/34[b] women (94.1%)

At delivery
OCR was **undetectable**[a] in 34/35[b] women (97.1%)



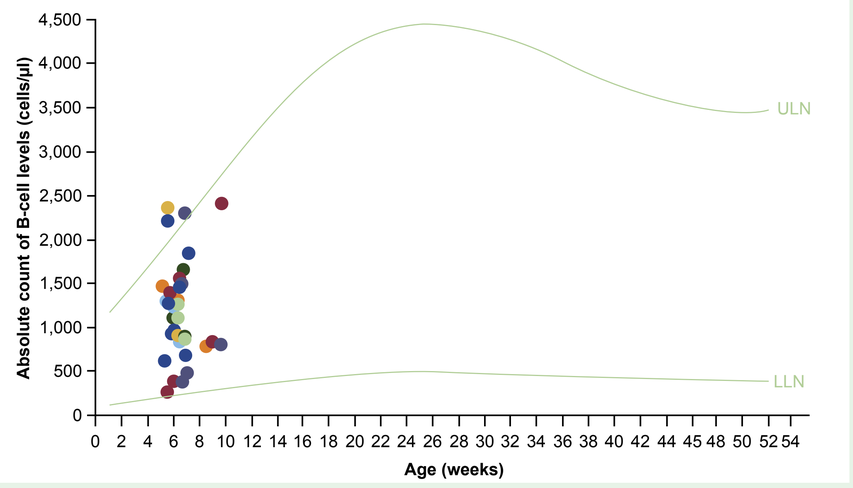
- **OCR levels in women were within the range of other OCR studies** and decreased with advanced gestational age
- OCR was undetectable in most women at **Week 35 (94.1%, 32/34[b]) and at delivery (97.1%, 34/35[b])**
- OCR was **undetectable in most umbilical cord serum** at birth (94.3%, 33/35[b]) and infant serum at Week 6 of life (97.0%, 32/33[b])
- Where detected in umbilical cord serum (n=2) and infant serum (n=1)
  - **OCR was close to the LLOQ (156 ng/ml) and well below therapeutic levels (200 µg/ml)[c]**
- **OCR levels in two cord-blood samples exceeded maternal OCR** levels at delivery, which is **in line with established IgG_1 evidence[2]**



At birth
OCR was **undetectable**[a] in 33/35[b] umbilical cord serum samples (94.3%)

Week 6
OCR was **undetectable**[a] in 32/33[b] of infant serum samples (97.0%)

Profile plots of infant B-cell levels at Week 6



All infant (34/34[b], 100%) B-cell levels were **above the age-specific lower limit of normal**

[a]Where OCR was detectable, it was close to LLOQ (LLOQ=156 ng/ml); [b]n/N; [c]The mean Cmax was 212 µg/ml (600 mg infusion over 3.5 hours) and 141 µg/ml (2 x 300 mg infusions over 2.5 hours administered within two weeks).[4,5]
Normal B-cell ranges in infants are defined by Borriello F, *et al.* 2022.[6]
CCOD: 8 April 2024.

Adverse Events Observed in Women

- AEs were expected as per the established OCR safety profile and/or occurring in pregnancy and postpartum as well as explainable by the COVID-19 pandemic

	Women (N=35)
Number of women with ≥1, n (%)	
AE	32 (91.4)
Serious AE	6 (17.1)
Number of women with ≥1, n (%)	
AE leading to treatment withdrawal[a]	1 (2.9)
AE leading to infusion modification/interruption	2 (5.7)
Related AE	9 (25.7)
Infections and infestations, n (%)	19 (54.3)
Injury, poisoning and procedural complications, n[b] (%)	10 (28.6)
Infusion-related reaction	3 (8.6)
Vulvovaginal injury	3 (8.6)
Perineal injury	2 (5.7)
Respiratory, thoracic and mediastinal disorders, n[b] (%)	5 (14.3)
Cough	4 (11.4)
Oropharyngeal pain	3 (8.6)

ALL RESOLVED

Overall, six women experienced six SAEs
- **Grade 3 AE in five women:** cholecystitis acute, 2x premature separation of placenta, post-procedural infection[c], uterine inflammation
- **Grade 4 AE in one woman:** postpartum haemorrhage
- **No SAEs occurred in pregnant women before labour**
- The majority occurred within 10 days after delivery
- There was an **equal distribution of SAEs** between ***in utero*- and non *in utero*-exposed** women
- **None were considered related to OCR**

- **19/35[d] (54.3%) women with a total of 42 infections**
- **COVID-19**, n=6 (17.1%)
- **Nasopharyngitis**, n=4 (11.4%)
- **Other infections**, n=2 (5.7%): conjunctivitis, sinusitis, URTI, UTI, vulvovaginal mycotic infection; n=1 (2.9%) cystitis, gastroenteritis, gastrointestinal viral infection, herpangina, hordeolum, influenza, nasal herpes, periorbital cellulitis, pharyngitis streptococcal, pneumonia, post procedural infection, respiratory tract infection, rhinitis
- **No serious COVID-19 infection occurred**

[a]Based on the Adverse Event eCRF page, where response to question 'Action taken with ocrelizumab due to SAE/AE' is 'Drug Withdrawn'. A non-serious Grade 2 AE of blood immunoglobulin G decreased (event occurred during pregnancy, resolved during the study) was initially reported in one woman. The woman did not resume OCR postpartum and switched to another MS DMT (ofatumumab). Lately reported, switching to another MS DMT (ofatumumab) was the reason for withdrawal and not a non-serious event of blood immunoglobulin G decreased; [b]Two or more events reported; [c]Due to caesarean; [d]n/N. Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
CCOD: 8 April 2024.

Adverse Events Observed in Infants

- Most AEs were mild (65.7%) to moderate (45.7%) and the pattern was comparable when stratified for *in utero* exposure
- Infections were typical of infancy[7]

	Infants (N=35)
Number of infants with ≥1, n (%)	
AE	26 (74.3)
Serious AE	4 (11.4)
Infections and infestations, n (%)	16 (45.7)
Respiratory, thoracic, mediastinal disorders, n[a] (%)	10 (28.6)
Nasal congestion	4 (11.4)
Cough	2 (5.7)
Oropharyngeal pain	2 (5.7)
Rhinorrhoea	2 (5.7)
Gastrointestinal disorders, n[a] (%)	9 (25.7)
Diarrhoea	4 (11.4)
Constipation	2 (5.7)
Gastroesophageal reflux disease	2 (5.7)

ALL RESOLVED

Overall, four infants experienced five SAEs
- **Grade 3 AE in three[b] infants:** neonatal infection and respiratory failure, heart rate decrease[c], RSV infection
- **Grade 4 AE in one infant:** cardiopulmonary failure[d]
- There was an equal distribution between ***in utero*- and non *in utero* exposed** infants
- **None were considered related to OCR**

16/35[e] (45.7%) infants with a total of 39 infections
- **Nasopharyngitis**, n=6 (17.1%)
- **Ear infection**, n=5 (14.3%)
- **Bronchitis**, n=5 (14.3%)
- **COVID-19**, n=4 (11.4%)
- **Conjunctivitis**, n=4 (11.4%)
- **RSV infection**, n=2 (5.7%)
- **Other infections**, n=1 (2.9%): bronchiolitis, bronchitis viral, candida infection, croup infectious, gastroenteritis, gastrointestinal infection, neonatal infection, otitis media, pharyngitis, rhinitis, subglottic laryngitis, tracheitis

[a]Two or more events reported; [b]A fourth infant with Grade 3 AE had a non-serious hyperbiliruminemia; [c]Post-CCOD follow up information – heart rate decrease was downgraded to non-serious AE and associated with mother's contraction due to oxytocin infusion; [d]Reported term: Cardio-respiratory insufficiency postpartal; [e]n/N. Investigator text for AEs encoded using MedDRA version 27.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
CCOD: 8 April 2024.

REFERENCES

1. Bove R, *et al. Mult Scler Relat Disord* 2022;64:103963.
2. Palmeira P, *et al. Clin Dev Immunol* 2012;2012:985646.
3. European Surveillance of Congenital Anomalies (EUROCAT) Guide 1.5. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en. Accessed August 2024.
4. Genentech, Inc. Available from: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed August 2024.
5. European Medicines Agency (EMA). Ocrevus: EPAR - Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf. Accessed August 2024.
6. Borriello F, *et al. J Allergy Clin Immunol* 2022;150:1216–1224.
7. Størdal K, *et al. J Pediatr Gastroenterol Nutr* 2017;65:225–231.

ABBREVIATIONS

AE, adverse event; **CA**, congenital anomaly; **CCOD**, clinical cut-off date; **COVID-19**, coronavirus disease 2019; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **EUROCAT**, European Surveillance of Congenital Anomalies; **GA**, gestational age; **IgG**, immunoglobulin G; **LLN**, lower limit of normal; **LLOQ**, lower limit of quantification; **LMP**, last menstrual period; **MMR**, measles, mumps and rubella; **MedDRA**, Medical Dictionary for Regulatory Activities; **MS**, multiple sclerosis; **OCR**, ocrelizumab; **RRMS**, relapsing-remitting multiple sclerosis; **RSV**, respiratory syncytial virus; **SAE**, serious adverse event; ULN, upper limit of normal; **URTI**, upper respiratory tract infection; **UTI**, urinary tract infection.

DISCLOSURES

K Hellwig has received grant/contract support, consultancy fees, honoraria and/or compensation from the Federal Innovationsfonds, National MS Society in Germany, Almirall, Bayer, Biogen, Sanofi, Teva, F. Hoffmann-La Roche Ltd, Novartis and Merck. **R Bove** has received consultancy fees from Alexion, EMD Serono, Horizon, Janssen, TG Therapeutics and Sanofi; and is funded by the National Multiple Sclerosis Society Harry Weaver Award, National Institutes of Health and Department of Defense, as well as Biogen, Eli Lilly, F. Hoffmann-La Roche Ltd and Novartis. **C Oreja-Guevara** received speaker and consultation fees from Alexion, Amgen, Biogen Idec, BMS, Horizon, Janssen, Merck, Novartis, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Sandoz, Viatris, Neuraxpharm and Teva Pharmaceuticals. **R Dobson** received research support from Multiple Sclerosis Society UK, Horne Family Foundation, Barts Charity, Merck, Biogen and Celgene; consultancy fees from F. Hoffmann-La Roche Ltd, Novartis, Sandoz and Biogen (all payments made were institutional and used to support research/educational activities); honoraria for lectures, speaking, etc. from Biogen, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck, Novartis, Janssen and Teva Pharmaceuticals; support for attending meetings and/or travel from Novartis, Biogen and Janssen (all payments made were institutional and used to support research/educational activities); and is part of the Association of British Neurologists MS Advisory Group and NHS England Clinical Reference Group. **E Maillart** reports research support from Biogen and personal fees for lectures and advisory boards from Alexion, Biogen, Horizon, Janssen, Merck, Novartis, Roche, Sanofi and Teva. **D Jacobs** has received consulting honoraria from Alexion, Banner Life Sciences, Biogen, Bristol Myers Squibb, Cycle Pharma, EMD Serono, Genentech, Inc., Horizon, Novartis, Sanofi-Genzyme and TG Therapeutics; and has received research support from Biogen, Genentech, Inc. and the University of California Los Angeles. **TF McElrath** has received research support from the National Institutes of Health and NX Prenatal Inc.; compensation for service on the scientific advisory boards of Mirvie Inc., F. Hoffmann-La Roche Ltd and Momenta Pharmaceuticals, Inc.; and consultancy fees from F. Hoffmann-La Roche Ltd and Comanche Biopharma. **C Pietrasanta** declares no competing interests. **H Kletzl**, **D Zecevic**, **C Raposo**, **L Craveiro**, **C-J Lin**, **N Pasquarelli** are employees of and shareholders in F. Hoffmann-La Roche Ltd. **A Kazlauskaite** is an employee of F. Hoffmann-La Roche Ltd. **S Vukusic** has received grants and research support from Biogen, Novartis, Merck-Serono, F. Hoffmann-La Roche Ltd and Sanofi-Genzyme; consultancy fees from F. Hoffmann-La Roche Ltd, Biogen, BMS-Celgene, Janssen, Novartis, Merck-Serono, Sanofi-Genzyme and Teva Pharma; and payment/honoraria for lectures, speaking etc. from F. Hoffmann-La Roche Ltd, Biogen, BMS-Celgene, Novartis, Merck-Serono, Sanofi-Genzyme and Teva Pharma.

ACKNOWLEDGEMENTS

We would like to thank all mothers and babies, as well as their families and the investigators participating in this study.
This study is sponsored by F. Hoffmann-La Roche Ltd;
writing and editorial assistance was provided by Nucleus Global and funded by F. Hoffmann-La Roche Ltd.

Presented at the 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 18–20 September 2024; Copenhagen, Denmark