2. SYNOPSIS

Title of Study:	Real-world safety of Copaxone in Offsprings of Breastfeeding and treated RMS pAtients – COBRA study
Protocol ID	TV44400-CNS-40159
Phase	Post-Marketing Phase IV, RWE
Study Objectives	To assess the outcome of offsprings during the initial period of up to 18 months of development who were breastfed by mothers undergoing GA treatment
Study Sites	Deutsches Multiple Sklerose und Kinderwunschregister Katholisches Klinikum Bochum gGmbH vertreten durch die Geschäftsführung Neurologische Universitätsklinik Prof. Dr. K. Hellwig St. Josef Hospital Klinikdirektor Prof. Dr. med. R. Gold Gudrunstrasse 56, 44791 Bochum
Study Design	Non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry.
Number of Study Patients	Planned: As this study is a non-interventional study designed for retrospective analysis of the clinical German MS and Pregnancy Registry, no power assessment was conducted. Actually enrolled: 120 breastfed offspring of which 60 were breastfed under maternal Copaxone therapy and 60 were breastfed without exposure to maternal disease modifying therapy
Study Population	Offspring of mothers with RMS who were breast feeding
Diagnosis and Main Criteria for Subject Selection	Mothers and their offspring who satisfied the following criteria: • Reported diagnosis of relapsing multiple sclerosis • Pregnancy resulted in live birth • Reported breastfeeding with either GA (GA Cohort) or with no DMT treatment (Control Cohort) • Gave informed consent and were enrolled into the German Multiple sclerosis and Pregnancy Registry
Study Procedures/Frequency	Not applicable
Study Duration	Up to 18 months period following childbirth
Study Timelines	Protocol sign off – 13 May 2020 Data analysis – 21 August 2020 Clinical study report – 3 November 2020
Study Endpoints:	Offspring Related Outcome Measures: • Frequency (no. of events) and incidence (no. of children with events) of hospitalizations. • Frequency and incidence of antibiotic treatments. • Growth parameters: weight, length and head circumference

	• Incidence of Pediatrician reports on children development delay (based on routinely measured parameters: turning, attempt to grasp, sitting, turning towards voices, first words, standing).
Statistical Analysis:	Statistical analyses were descriptive in nature. Therefore, no formal hypotheses testing are planned for the study outcome measures. • Summary statistics of study outcome measures were displayed by both study cohorts (GA Cohort and Control Cohort) and overall. Potential lack of balance in risk factors between study cohorts were assessed using a by cohort, side-by-side display of descriptive statistics of the risk factors and their 95% confidence intervals. • Incidence tables of binary outcome measures (e.g. proportion of children hospitalized) provided the No. of participants with events and relative percentages as well as the 95% two-sided confidence intervals.. • Frequency tables of events (e.g. No. of hospitalizations, No. of relapses) display the annualized number of events as well as its two-sided 95% confidence interval. • Descriptive statistics of continuous outcome measures (e.g. weight, head circumference) at end of follow-up duration will include N, mean, SD, SE, Median, IQR min and max values.
Summary of Results	Data were available and analysed for 60 GA cohort children (n=58 women; n=59 pregnancies) and 60 Control cohort children (n=60 women; n=60 pregnancies) during a postpartum period of up to 18-months. Demographics and MS prognostic factors of mothers in both cohorts were descriptively comparable. 86.7% of mothers in the GA cohort as compared to 25.0% in the Control cohort were treated with GA also during pregnancy, showing that the "cumulative" GA exposure risk (during pregnancy and breastfeeding period) was higher than the risk of GA exposure limited to the brestfeeding period only. Offspring safety outcomes were comparable between the two cohorts for the annualized hospitalisation rates, annualized antibiotic treatments rates and proportions of children with diagnosed developmental delay at 12 months. In terms of development measures, growth parameters (body weight, body length and head circumference) were comparable between cohorts, however, 5% of Control cohort (n=3) were diagnosed with developmental delays, compared with none in the GA cohort, all suggesting no evidence of enhanced risk to offspring due to Copaxone treatment during breastfeeding period.
Conclusions	No evidence was found that maternal treatment with Copaxone during breastfeeding adversely affect offspring's body measurements, incidences of developmental delay, and frequency and incidences of hospitalisations or use of antibiotic treatments.