# Multinational observational before-and-after study of clinical outcomes after introduction of NeoMega36 fatty-acid supplementation in extremely preterm infants

V. 2.1

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# Multinational observational before-and-after study of clinical outcomes after introduction of NeoMega36 fatty-acid supplementation in extremely preterm infants

**Protocol / Project plan (for participating neonatal units)**
**Acronym:** NeoMega-REAL
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**Coordinating centre:** University of Gothenburg, Sweden
**Coordinating PI:** Anders K Nilsson, Docent, Institute of Neuroscience and Physiology Department of Clinical Neuroscience
**Data manager / statistics:** Aldina Pivodic
**Contact email:** anders.k.nilsson@gu.se
**Registration:** ClinicalTrials.gov (NCT number to be added after registration)

**Version history**

- 1.0 (2026-02-03): submitted with the ethics application (reference number 2026-02384-01).
- 2.0 (2026-06-01, sent to centers 2026-06-16): revised after the investigator meeting on 2026-05-12. Infants born at 22+0 to 27+6 weeks reported by gestational week; BPD classified by Jensen grade; composite outcomes added; local nutrition data added; NeoMega36 given/not-given counts used descriptively only.
- 2.1 (2026-10-21): severe ROP specified as the single primary outcome, with treated ROP and any ROP as secondary outcomes; timeline and ethics sections updated; editorial corrections before registration at ClinicalTrials.gov.

## 1. Background and rationale

Long-chain polyunsaturated fatty acids (LCPUFAs), particularly docosahexaenoic acid (DHA) and arachidonic acid (ARA), are important for neurodevelopment and retinal maturation. Extremely preterm infants miss the substantial third-trimester placental

transfer and standard postnatal nutrition often does not fully compensate, resulting in low circulating ARA/DHA levels in the neonatal period.

Randomized clinical trials have evaluated enteral ARA/DHA supplementation in extremely/very preterm infants. In the Mega Donna Mega trial, enteral supplementation with ARA and DHA was associated with a ~50% reduction in severe retinopathy of prematurity (ROP) and in secondary outcomes related to brain development. A similar supplement has now been introduced for clinical use as NeoMega36® (Neobiomics, Solna, Sweden).

NeoMega36 is currently used in several European countries. To assess real-world outcomes following implementation across diverse clinical settings, we will perform a multicenter observational follow-up study using aggregated routine morbidity.

## 2. Objectives and research questions

### 2.1 Primary objective

To evaluate whether the implementation of NeoMega36 in routine care is associated with a reduction in severe ROP (ROP stage 3 or greater and/or ROP treatment) in infants born before 28 completed gestational weeks (22+0 to 27+6 weeks) with final ROP screening outcome (survivors).

In the multinational European component, this will be studied across different sites/countries using aggregated routine morbidity data and meta-analytic methods. Additionally in the Swedish component, this will be studied using linked national quality register data.

### 2.2 Secondary objectives

To evaluate whether implementation of NeoMega36 in infants born before 28 completed gestational weeks is associated with changes in:

- Treated ROP and any ROP
- Bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age (PMA), classified according to respiratory support level using the Jensen et al. definition
- Necrotizing enterocolitis (NEC), including surgical NEC where available
- Mortality and composite morbidity/death outcomes, particularly BPD or death and NEC or death

To support interpretation of outcomes across centers, the study will also collect information on local nutritional strategies and potential sources of ARA/DHA other than NeoMega36, such as milk fortifiers and preterm formula.

A longer-term exploratory objective is to assess whether implementation of NeoMega36® is associated with differences in neurodevelopmental outcomes within routine clinical follow-up, when such data become available.

## 3. Study design

**European observational component**
Multicenter, observational "before/after implementation" study using aggregated group-level routine data from participating neonatal units.

The primary comparison will be between a historical period before NeoMega36 implementation and a NeoMega period after implementation, including all eligible infants born at 22+0 to 27+6 weeks gestation. The analysis will focus on period-level implementation rather than individual treatment receipt.

Within the NeoMega period, centers may report the number of eligible infants who received NeoMega36 and the number who did not receive NeoMega36 to describe implementation coverage and local practice. These given/not-given data will not be used as a main comparative morbidity analysis, because individual receipt of the supplement may be influenced by clinical factors such as gastrointestinal problems, temporary nil per os status, or other contraindications.

No intervention, randomization, additional visits, or additional clinical procedures are introduced by the study.

As this is a before–after implementation study, observed differences between periods cannot be assumed to be solely attributable to NeoMega36 implementation. Changes in clinical practice, case mix, survival rates, nutritional strategies, and other temporal factors may also influence outcomes. The study is therefore designed to evaluate outcomes following implementation in routine care rather than to estimate a causal treatment effect of NeoMega36 at the individual patient level.

**Swedish register-based component**
In addition to the multinational aggregated-data component, the study includes a Swedish register-based observational cohort. For the Swedish part, coded individual-level data, in which the register holder holds the code key, will be retrieved from national quality registers and analyzed within Sweden. No intervention, randomization, additional visits, or additional clinical procedures will be introduced. NeoMega36 is provided as part of routine clinical care, independent of the research project. The Swedish component will enable evaluation of short- and long-term outcomes after implementation of NeoMega36 at a population level and allow adjustment for relevant background factors not available in the aggregated multinational dataset.

## 4. Setting and participating centers

Participating centers are neonatal units in Europe that have implemented NeoMega36 as part of routine care. Each center will designate:

- a **Local PI** (clinical lead)
- a **Data contact** (person responsible for extracting/aggregating data and completing the template)

The same person can be both local PI and data contact.

## 5. Study population

**European study population**

The study population comprises preterm infants born from 22+0 to 27+6 gestational weeks and cared for at the participating center during:

- a **Historical period** (before implementation), for preferably 24 months, and
- a **NeoMega period** (after implementation), at least 12 months

Data will be provided by gestational week at birth:

- 22+0 to 22+6 weeks
- 23+0 to 23+6 weeks
- 24+0 to 24+6 weeks
- 25+0 to 25+6 weeks
- 26+0 to 26+6 weeks
- 27+0 to 27+6 weeks
- **All infants** (overall row)

Centers that do not routinely treat or screen infants in a particular gestational week should mark the relevant cells as not applicable or zero, as appropriate, in the data extraction sheet.

**Swedish study population**

The Swedish study population will include all infants born before 28 completed gestational weeks and cared for at Swedish neonatal units during defined periods before and after implementation of NeoMega36. Inclusion will be population-based through national registers. No individual-level exclusion criteria are planned, apart from lack of relevant register data for the outcomes under study.

## 6. Exposure definition

The primary exposure in the European component is center-level implementation of NeoMega36 in routine care. A center enters the NeoMega period after local implementation of NeoMega36 according to local clinical practice.

For each center, the following implementation information will be collected:

- NeoMega36 implementation date and start/stop dates for the data collection periods
- local eligibility criteria for NeoMega36
- local dose regimen, starting criteria, stopping criteria, and handling of interruptions
- a brief description of common reasons for not giving NeoMega36, if this can be provided without individual-level data

The given/not-given counts are intended to describe uptake and implementation fidelity. They are not intended to define the primary comparative exposure for the European morbidity analyses.

## 7. Outcomes

All outcomes are reported as **counts (N)** per period and gestational week. Where possible, centers should apply the same local definitions across the Historical and NeoMega periods and should report any definition changes during the study periods.

### 7.1 Primary outcome

The primary outcome is severe ROP, classified according to ICROP/ETROP-based practice:

- **Severe ROP, N:** number of infants with **ROP stage 3 or greater and/or ROP treatment**.

The sample size calculation (section 11.1.4) is based on this outcome. Treated ROP and any ROP are secondary outcomes (section 7.2). For all ROP outcomes, the following is reported as the denominator:

- **Screened for ROP, N**: number of infants who underwent ROP screening at the center during the specified period and gestational week, in line with local screening guidelines

*Note:* “Severe ROP”, “Treated ROP”, and “Any ROP” may overlap; all three variables are collected to enable consistent reporting across centers and flexible analysis.

### 7.2 Secondary outcomes

- **Treated ROP, N:** number of infants who received ROP treatment, such as anti-VEGF and/or laser, regardless of stage/type, per local practice
- **Any ROP, N:** number of infants who developed any stage of ROP.
- **BPD at 36 weeks PMA, N**, classified using the Jensen et al. respiratory-support-based definition: no BPD, no support; grade 1, nasal cannula at 2 L/min or less; grade 2, nasal cannula above 2 L/min or non-invasive positive airway pressure; grade 3, invasive mechanical ventilation.
- **BPD or death, N**: number of infants with BPD at 36 weeks PMA or death before BPD assessment, counted once in the composite outcome.
- **NEC, N**: number of infants with NEC as documented in routine care; surgical NEC should be reported separately where available.
- **NEC or death,** N: number of infants with NEC or death before discharge, counted once in the composite outcome.
- **Death before discharge, N**, and, where feasible, death before ROP screening or before 36 weeks PMA.

Composite outcomes are included to reduce ambiguity when death and morbidity occur in the same infant or when death precludes later outcome assessment.

## 8. Data collection

### 8.1 European Data Collection

#### 8.1.1 What centers will submit

Centers will complete an Excel template (**“NeoMega-REAL Datasheet Template”**).

The template collects, for each gestational week and period:

- start date and stop date per respective period
- total number of eligible infants born at 22+0 to 27+6 weeks
- screened for ROP, N
- severe ROP, N
- treated ROP, N
- any ROP, N
- BPD at 36 weeks PMA by Jensen grade, N
- NEC, N, with surgical NEC reported separately where available

- death before discharge, N
- BPD or death, N
- NEC or death, N
- NeoMega36 implementation and uptake information during the NeoMega period

The template will also collect center-level contextual information during each period, including nutrition practices and other major clinical practice changes, including:

- use of human milk fortifiers and whether fortifiers contain DHA and/or ARA
- use of preterm formula and whether the formula contains DHA and/or ARA
- routine lipid, fatty-acid, or other nutritional supplements relevant to DHA/ARA exposure
- major changes in feeding protocols or fortification practices between the Historical and NeoMega periods
- other major changes in clinical practice or unit protocols that are expected to affect morbidity frequencies

### 8.1.2 Period definitions

- **Historical period**: period before local implementation of NeoMega36 and not overlapping the NeoMega period. Preferably, the historical period should be long enough to provide stable estimates and should be approximately twice the length of the NeoMega period where feasible.
- NeoMega period: begins after local implementation of NeoMega36. Centers specify start and stop dates.
- NeoMega given/not given: if available, centers report counts to describe uptake, implementation coverage, and reasons for non-use at the aggregate level. These categories are descriptive and not the main comparative groups for morbidity outcomes.

### 8.1.3 Data level and identifiers

Centers will submit **aggregated counts only**. No individual-level data, no dates of birth, no patient identifiers, and no code keys will be collected.

### 8.1.4 Submission process

- Each center completes the Excel template and returns it to the coordinating center via the agreed secure transfer method.
- Coordinating center will provide a **secure upload route** and instructions.

### 8.2 Swedish Register Data Collection

For the Swedish component, no primary data collection from participants will be performed. Data will be retrieved from the Swedish Neonatal Quality Register (SNQ) and SWEDROP, the Swedish national ROP quality register. SNQ will provide information on neonatal characteristics, NeoMega36 exposure, and neonatal morbidity, while SWEDROP will provide data on ROP screening, disease severity, and treatment. Register linkage will be used to evaluate the occurrence of prematurity-related complications before and after implementation of NeoMega36 in routine care.

The primary Swedish outcome will be severe ROP; secondary outcomes include treated ROP, any ROP, BPD, and NEC. On a longer-term basis, neurodevelopmental follow-up outcomes from routine clinical follow-up programs may be evaluated in the Swedish cohort. Depending on data availability, additional neonatal outcomes relevant to safety monitoring may also be explored in the Swedish cohort.

No extra examinations, sampling procedures, visits, or contacts with children or guardians will occur in the Swedish component.

## 9. Data management and security

For the European component, received files containing aggregated group-level data will be stored with restricted access on the University of Gothenburg secure storage system (Nextcloud). Only authorized project members will have access. Files will be version-controlled, and a data query log will document any clarifications or corrections.

For the Swedish register-based component, pseudonymized individual-level data retrieved from national quality registers will be stored and analyzed separately within secure systems at the University of Gothenburg, with access restricted to authorized study personnel. Any key linking study data to personal identifiers will be stored by the SNQ register holder.

## 10. Data quality assurance

To ensure consistency and reliability:

- Centers use a standardized template with predefined GA strata and outcomes.
- The coordinating center will perform plausibility, for example:
    - Treated ROP ≤ Screened
    - Severe ROP ≤ Screened
    - Any ROP ≤ Screened

    - BPD grade counts are internally consistent with the total number of eligible infants alive at 36 weeks PMA, where this denominator is available
    - composite outcome counts are not lower than their component morbidity counts
    - NeoMega given + NeoMega not given ≈ NeoMega total (within ROP screened)
    - Period dates are complete and non-overlapping
- Any inconsistencies will be addressed via queries to the center and documented in a query log.

# 11. Statistical analysis plan

## 11.1 European data

Analyses will use aggregated center-level counts.

Analyses of the implementation period (after vs before) and binary outcomes will be performed using a two-stage approach. Within each participating center, GA-adjusted odds ratios (OR) will be estimated using the aggregated counts. Center-specific results will then be pooled using random-effects meta-analysis to account for between-center heterogeneity. As a sensitivity analysis, a binomial mixed-effects model with logit-link function will be performed on aggregated data, including gestational age strata as fixed effects and neonatal unit as a random effect.

### 11.1.1 Primary analysis: before vs after implementation

For the primary outcome (severe ROP), and in the same way for each secondary outcome, we will compare occurrence between the Historical and NeoMega periods:

- overall for all infants born 22+0 to 27+6 weeks
- stratified by gestational week where data allow

Analyses will account for center-level variation as per the methods above. Potential heterogeneity between participating centers may arise from differences in patient populations, survival rates among extremely preterm infants, ROP screening practices, treatment strategies, nutritional protocols, and implementation procedures. Between-center heterogeneity will therefore be assessed using standard random-effects meta-analytic measures, including the $I^2$ statistic where appropriate.

### 11.1.2 Secondary and descriptive analyses

Secondary analyses will evaluate treated ROP, any ROP, BPD, NEC, death, and the composite outcomes BPD or death and NEC or death. These outcomes will be analyzed using the same before/after implementation framework as the primary analysis, where data completeness and event frequencies allow.

NeoMega36 given/not-given counts within the NeoMega period will be summarized descriptively to report implementation coverage. Direct morbidity comparisons between infants given and not given NeoMega36 during the NeoMega period will not be interpreted as causal because treatment receipt may be affected by clinical condition, feeding tolerance, or temporary nil per os status.

Center-level nutrition variables will be summarized to describe background exposure to DHA/ARA and other relevant nutritional strategies. Where feasible, sensitivity analyses may explore whether results differ according to major differences in nutritional practice or major changes between periods.

### 11.1.3 Sensitivity / robustness

Where feasible, sensitivity analyses will include:

- Analyses restricted to centers with comparable period lengths and stable screening criteria
- analyses excluding gestational weeks or centers with sparse counts, where sparse data materially affect model stability
- analyses using alternative denominators for ROP outcomes, such as screened infants versus all eligible liveborn/admitted infants, where available

### 11.1.4 Sample size

This is a pragmatic, real-world multicenter study. In the first phase, we anticipate approximately ~200-300 infants per period (historical vs NeoMega) across participating sites, with power primarily for moderate-to-large differences in outcomes; estimates will be reported with confidence intervals.

Based on Swedish data, a formal sample size calculation for severe ROP showed that 151 infants per group (historical and NeoMega cohorts) are required to achieve 80% power ($\alpha = 0.05$, two-sided; allocation ratio 1:1), assuming a severe ROP incidence of 27.1% among infants born at <28 weeks' gestation and a 50% reduction in the NeoMega cohort.

## 11.2 Swedish analyses

The Swedish register-based cohort will be analyzed separately from the multinational aggregated-data analyses. Outcome frequencies before and after implementation of NeoMega36 will be compared overall and stratified by gestational age where relevant. Depending on data completeness and outcome frequencies, regression models will be used to adjust for relevant background characteristics and calendar period. Results from the Swedish component may be reported separately and, where appropriate, interpreted alongside the multinational findings as complementary evidence.

# 12. Ethics and regulatory considerations

This project involves no intervention. In the multinational European component, no individual-level personal data are collected by the coordinating center and only aggregated group-level data will be analyzed. The Swedish register-based component uses coded individual-level register data, as described below.

The Swedish coordinating team has ethics approval from the Swedish Ethical Review Authority to receive and analyze aggregated data from the participating centers and to retrieve and analyze Swedish register data (approved 2026-04-29). Title: "Multinational follow-up study after the introduction of fatty-acid supplementation in preterm infants"; reference number: 2026-02384-01.

**Each participating center is responsible for:**

- assessing whether local approvals are required for sharing aggregated routine data, and
- obtaining any necessary institutional/regulatory permissions in accordance with local rules.

**Ethics and regulatory considerations for the Swedish component**
The Swedish component is a register-based observational study using individual-level data from established national quality registers. No intervention, no change in clinical management, and no direct contact with participants or guardians will occur within the study. The main risk is a low risk of privacy intrusion associated with the handling of register data. This risk is minimized through pseudonymization, restricted access, secure data storage, and reporting of results only at group level. Ethical approval for the register-based component has been obtained (reference number 2026-02384-01). Any further permissions required for data retrieval, such as approval from the register holders, will be obtained before data are retrieved.

## 13. Dissemination and publication policy

Results will be disseminated through:

- Peer-reviewed scientific publication(s)
- Conference presentations
- Feedback summary to participating centers

Authorship will follow ICMJE recommendations. Participating centers contributing data and engaging in manuscript review will be eligible for co-authorship (or group authorship model), based on pre-specified contribution criteria shared in advance.

## 14. Roles and responsibilities

### Coordinating center (University of Gothenburg)

- Provide template and instructions
- Secure data receipt and storage
- Data quality checks and queries
- Statistical analysis and reporting
- Draft manuscript(s) and coordinate review

### Participating centers

- Identify local implementation date/periods
- Extract and aggregate routine data per template
- Ensure local compliance/permissions
- Respond to data queries
- Participate in interpretation and manuscript review (as applicable)

## 15. Timeline

**European component:**

- Data collection from centers: 2026-06-16 to 2027-07-31
- Data cleaning + statistical analyses: 2027-02-01 to 2027-03-31
- Manuscript preparation and submission: 2027-04-01 to 2027-09-30

**Swedish component:**

- Start of routine clinical implementation of NeoMega36® in Sweden: Q3 2026
- Register-based follow-up after implementation: register data collection from 2026-08-01 to 2031-08-01
- First register extraction and data linkage: Q3 2027

- First analyses of neonatal outcomes: Q4 2027-Q1 2028
- Manuscript preparation and submission: 2028
- Possible neurodevelopmental follow-up at about 5 years of age; planned end of project: 2036-03-31

## 16. Contact details

**Coordinating PI:** Anders K. Nilsson, Docent, Researcher
University of Gothenburg
Institute of Neuroscience and Physiology, Department of Clinical Neuroscience

**Email:** anders.k.nilsson@gu.se

**Data contact:** Aldina Pivodic, aldina.pivodic@gu.se

## 17. Appendices

- Appendix A: NeoMega-REAL Datasheet Template v2.0, European (Excel)
- Appendix B: Center-level nutrition practice questions

## 18. References

Hellström A, Nilsson AK, Wackernagel D, et al. Effect of Enteral Lipid Supplement on Severe Retinopathy of Prematurity: A Randomized Clinical Trial. JAMA Pediatrics. 2021;175(4):359-367. doi:10.1001/jamapediatrics.2020.5653

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