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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
## STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>Name of sponsor/company:</th>
<th>Individual Study Table Referring to Part of the Dossier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premacure AB, A Member of the Shire Group of Companies</td>
<td>(for National Authority Use only)</td>
</tr>
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<table>
<thead>
<tr>
<th>Name of finished product:</th>
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<tbody>
<tr>
<td>Mecasermin rinfabate</td>
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<table>
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<tr>
<th>Name of active ingredient:</th>
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<tbody>
<tr>
<td>rhIGF-1/rhIGFBP-3</td>
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<table>
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<tr>
<td>Determination of the rhIGF-1/rhIGFBP-3 Dose, Administered as a Continuous Infusion, Required to Establish and Maintain Longitudinal Serum IGF-1 Levels Within Physiological Levels in Premature Infants, to Prevent Retinopathy of Prematurity</td>
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A Phase 2, Randomized Controlled, Assessor-blind, Dose-confirming, Pharmacokinetic, Safety and Efficacy, Multicenter Study

<table>
<thead>
<tr>
<th>Investigators:</th>
<th>Multicenter, , Coordinating Investigator (Section D)</th>
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<tbody>
<tr>
<td></td>
<td>Sweden</td>
</tr>
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<table>
<thead>
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<th>Study center(s):</th>
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<tbody>
<tr>
<td>A total of 20 sites in Italy, the Netherlands, Poland, Sweden, the United Kingdom and the United States enrolled subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publications (references):</th>
<th>Section D</th>
</tr>
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<table>
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<th>Study period:</th>
<th>Phase of development:</th>
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<tr>
<td>18 Jun 2010-30 Mar 2016 (Overall)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>19 Sep 2014-30 Mar 2016 (Section D only)</td>
<td></td>
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</tbody>
</table>
Name of sponsor/company: Premacure AB, A Member of the Shire Group of Companies

Name of finished product: Mecasermin rinfabate

Name of active ingredient: rhIGF-1/rhIGFBP-3

Objectives:
Objectives of Sections A, B, and C
The primary objectives of study Sections A, B and C were:

Study Section A
- To establish the dose and sampling schedule to be used in Study Sections B and C.

Study Sections B and C
- To determine the dose of rhIGF-1/rhIGFBP-3, administered by continuous IV infusion, required to reach and maintain over time a physiological range, defined as the in utero levels for corresponding gestational age in a normal population (20-60 μg/L), in preterm infants (Langford et al. 1998).
- To determine serum concentration of IGF-1 and associated pharmacokinetic parameters after continuous IV infusion of rhIGF-1/rhIGFBP-3.

Secondary Objective of Sections A, B, and C
The secondary objective of study Sections A, B, and C was

- Follow up of safety and efficacy parameters

Objectives of Section D
Primary Objectives
The primary objectives of study Section D were:

- To determine the effect of rhIGF-1/rhIGFBP-3 on the severity of ROP as compared to the severity of ROP in an untreated control population.

- To evaluate the dose of rhIGF-1/rhIGFBP-3, administered by continuous IV infusion, required to reach and maintain a physiological range of serum IGF-1 of 28-109 μg/L, defined as the in utero levels of IGF-1 for corresponding GA in a normal population, as described in Shire Reports 725-ROP-13-2103 and 725-ROP-13-2113.

- To determine serum concentrations of IGF-1 and associated pharmacokinetic parameters after continuous IV infusion of rhIGF-1/rhIGFBP-3.

- To determine serum concentration of IGFBP-3 and acid labile subunit (ALS) after continuous IV infusion of rhIGF-1/rhIGFBP-3.

The secondary objective of study Section D was:

- To determine the effect of rhIGF-1/rhIGFBP-3 on other efficacy parameters and determine the safety profile of rhIGF-1/rhIGFBP-3 when compared with standard neonatal care in preterm infants.
### Methodology

The study was designed in 4 sections that were conducted sequentially. The last section, Section D, the focus of the results discussion, was a controlled (Standard of Care), randomized trial with assessors of the primary endpoint masked to the treatment status of each subject. Two interim analyses were planned and conducted. The first was a pharmacokinetic analysis conducted when 10 treated subjects had completed the rhIGF-1/rhIGFBP-3 dosing phase of the study to assess the appropriateness of the target dose. In the second, a conditional power analysis was performed on unmasked data, by an external independent statistician. The purpose of this second analysis was to assess the appropriateness of the sample size and assumptions made regarding the distribution of the maximum severity of ROP.

### Number of subjects (planned and analyzed):

120 subjects were planned to be randomized 1:1 to rhIGF-1/rhIGFBP-3 or Standard of Care.

Sixty-one subjects were randomized to rhIGF-1/rhIGFBP-3; 46 (75.4%) subjects completed the study. All 61 subjects were included in efficacy (Full Analysis Set [FAS]), safety (Safety Analysis Set) and pharmacokinetic (PK Analysis Set) analyses. A subset of subjects who met at least 70% of IGF-1 levels within the target range (28-109 μg/L), and who received at least 70% duration of infusion of rhIGF-1/rhIGFBP-3, were included in an Evaluable Set.

Sixty subjects were randomized to Standard of Care; 46 (76.7%) subjects completed the study. All 60 subjects were included in efficacy (FAS) and safety (Safety Analysis Set) analyses.

### Diagnosis and main criteria for inclusion:

Subject must have been between GA of 26 weeks + 0 days and 27 weeks + 6 days (Study Section A) or between GA of 23 weeks + 0 days and 27 weeks + 6 days (Study Sections B, C, and D), inclusive.

Subjects were excluded if:

- born small for gestational age (SGA), ie, body weight at birth <-2 standard deviation score (SDS) (Study Section A only)
- monozygotic twins
- had a detectable gross malformation
- had a known or suspected chromosomal abnormality, genetic disorder, or syndrome, according to the investigator’s opinion
- had persistent blood glucose level <2.5 mmol/L or >10 mmol/L at Study Day 0
- had an anticipated need for administration of erythropoietin
- there had been maternal diabetes requiring insulin during the pregnancy
- had clinically significant neurological disease, according to the investigator’s opinion (Stage 1 IVH allowed)
**Name of sponsor/company:** Premacure AB, A Member of the Shire Group of Companies

**Name of finished product:** Mecasermin rinfabate

**Name of active ingredient:** rhIGF-1/rhIGFBP-3

**Investigational product, dose, mode of administration, and batch number(s):**
rhIGF-1/rhIGFBP-3 (mecasermin rinfabate) administered as a continuous intravenous infusion at a dose of 250 $\mu$g/kg/24 hours

Lot Numbers for Section D: [redacted]

**Reference product(s), dose, mode of administration, and batch number(s):** None.

**Duration of treatment:** Continuous infusion began the day of birth to PMA 29 weeks + 6 days.

**Criteria for evaluation (Section D):**
- Maintenance of serum IGF-1 levels within a pre-specified physiological target range (28-109 $\mu$g/L)
- Maximum severity of retinopathy of prematurity (ROP) across all examinations by a centralized pediatric ophthalmologist
- Time to discharge from neonatal intensive care
- Severity of bronchopulmonary dysplasia (BPD) (none, mild, moderate, severe) as assessed by oxygen requirement during the first 28 days of life with $O_2$ challenge test at PMA 36 weeks ± 3 days to distinguish between moderate and severe BPD
- Change in growth parameters of weight, height and head circumference
- Brain growth parameters measured by ultrasound (volumes) or magnetic resonance imaging (MRI)
- Development and severity of IVH as assessed by cerebral ultrasound
- Adverse events (including serious adverse events and pre-specified events of special interest)
- Clinical chemistry, hematology and blood gas results
- Abnormal blood glucose values
- Development of anti-IGF-1/IGFBP-3 antibodies
- Vital signs
- Results of physical examinations, including the development of tonsillar hypertrophy
Name of sponsor/company: Premacure AB, A Member of the Shire Group of Companies

Name of finished product: Mecasermin rinfabate

Name of active ingredient: rhIGF-1/rhIGFBP-3

Statistical methods (Section D):
The primary endpoint, maximum severity of ROP evaluated by a centralized pediatric ophthalmologist using RetCam images, was analyzed using a generalized CMH row means score statistic with modified -ridit scores (the van Elteren test), adjusting for GA strata. The null hypothesis was that the distribution of maximum severity of ROP stage across all retinal examinations between the active treatment group and the Standard of Care group were the same. Supportive and sensitivity analyses for the endpoint included analysis by an aligned rank test, repeating the analyses for the Evaluable Set and repeating the analyses for severity of ROP evaluated by the local pediatric ophthalmologist. Sensitivity analyses using distribution-based imputation and multiple imputations for subjects missing all ROP assessments were also performed.

The difference in TDNIC was tested using the stratified version of the Wilcoxon rank-sum test, adjusted for gestational age (GA) status. The median treatment difference was calculated using the Hodges-Lehman estimate of the difference in the 2 medians.

Analysis of the distribution of BPD and IVH was similar to that of the primary endpoint.

Weight, height, brain volumes and head circumference were analyzed using linear mixed model repeated measurement analysis.

Safety parameters were summarized descriptively.

Results (Section D):
Disposition:
One hundred twenty-one subjects were randomized to either rhIGF-1/rhIGFBP-3 or standard neonatal care. The proportion of subjects who completed the study was similar between the rhIGF-1/rhIGFBP-3 (n=46, 75.4%) and Standard of Care (n=46, 76.7%) groups. The most common reason for premature discontinuation was an AE, and most of these AEs leading to discontinuation had a fatal outcome. In the rhIGF-1/rhIGFBP-3 group 11 (18.0%) subjects discontinued due to a SAE with fatal outcome. In addition, 1 subject in the group had an SAE with a fatal outcome, although the primary reason for discontinuation was withdrawal of consent. Thus, a total of 12 (19.7%) subjects in the rhIGF-1/rhIGFBP-3 group died during the study. In the Standard of Care group, 9 subjects discontinued the study due to an AE, and of these, 7 (11.7%) discontinuations were due to SAEs with a fatal outcome.

The rhIGF-1/rhIGFBP-3 and Standard of Care groups were similar in the distribution of sex, with males comprising 63.9% and 65.0% of the rhIGF-1/rhIGFBP-3 and Standard of Care groups, respectively. The 2 groups were also similar in mean gestational age (25.60 and 25.62 weeks), however, the rhIGF-1/rhIGFBP-3 had 3 more subjects in the <26 Weeks subgroup and 2 fewer subjects in the older gestational age group (≥26 Weeks) than the Standard of Care group. White infants comprised 80.3% and 70.0%, and Black or African American infants comprised 8.2% and 15% of the rhIGF-1/rhIGFBP-3 and Standard of Care groups, respectively. The 2 groups were balanced with respect to Asian infants, 4 (6.6%) infants in the rhIGF-1/rhIGFBP-3 group and 5 (8.3%) infants in the Standard of Care group.

APGAR scores were similar between the 2 groups at 1 minute (4.80 vs 4.88), 5 minutes (7.00 vs 6.95), and 10 minutes (7.89 vs 7.87). The mean weight was less in the rhIGF-1/rhIGFBP-3 group (0.780 vs 0.804 kg), possibly reflecting the inclusion of 3 more infants in the younger gestational age subgroup and 2 fewer infants in the older gestational age subgroup than in the Standard of Care group. The mean weight is less in
the rhIGF-1/rhIGFBP-3 group in both the < 26 Weeks GA subgroup (0.685 vs 0.709) and ≥26 Weeks GA subgroup (0.907 vs 0.914), although these differences were not statistically significant. Fifty-nine per cent of the infants in the rhIGF-1/rhIGFBP-3 group and 55.0% in the Standard of Care group were delivered by Cesarian section. In the <26 Weeks gestational age group, the rhIGF-1/rhIGFBP-3 group had 20 (57.1%) deliveries by Cesarian section, with 13 (40.6%) Cesarian sections in the Standard of Care group. In the ≥26 Weeks gestational age group, the rhIGF-1/rhIGFBP-3 group had 16 (61.5%) deliveries by Cesarian section with 20 (71.4%) Cesarian sections in the Standard of Care group. Any differences between the 2 groups in these baseline characteristics were not statistically significant.

Overall, maternal and perinatal histories were similar between the rhIGF-1/rhIGFBP-3 group and the Standard of Care group, although there were a few more mothers with a clinical diagnosis of chorioamnionitis in the rhIGF-1/rhIGFBP-3 group (16.4% vs 10.0%). However, fewer mothers in the rhIGF-1/rhIGFBP-3 group were treated with maternal antibiotics (52.5% vs 63.3%) and less reported other maternal infections (18% vs 23.3%). Rates of pre-eclampsia, premature rupture of membranes and receipt of fertility therapy were similar between the two groups. In the <26 Weeks group, there were more mothers who had received fertility therapy in the rhIGF-1/rhIGFBP-3 group than the standard of care group (25.7% vs. 6.3%) and more had been diagnosed with pre-eclampsia (11.4% vs 0). More infants in the rhIGF-1/rhIGFBP-3 group were in fetal distress prior to delivery as indicated by the percentage with pathological cardiotocography (16.4% vs 6.7%).

Pharmacokinetic results:

For rhIGF-1/rhIGFBP-3 treated subjects, the majority (66%) of serum IGF-1 levels were above the lower bounds of the target range while for Standard of Care subjects the majority of serum IGF-1 levels were below the target range.

Efficacy results:

Primary:

The difference between the 2 treatment groups in the distribution of the maximum severity of ROP was not statistically significant (p=0.0642) for the FAS. This was confirmed in the Evaluable Set (p=0.2392) as well as in each supportive or sensitivity analysis of the primary endpoint. However, numerically, there were a larger proportion of subjects with Stage 3 or 3+ ROP and a smaller percentage of subjects with no ROP (Stage 0) compared to Standard of Care group. Results of analyses of the Evaluable Set, and the evaluations of the local pediatric ophthalmologist and other supportive and sensitivity analyses confirmed the primary analysis, which was performed based on the central reading of the RetCam images.

### Maximum Severity of ROP Evaluated by Central Pediatric Ophthalmologist

<table>
<thead>
<tr>
<th></th>
<th>rhIGF-1/rhIGFBP-3</th>
<th>Standard of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FAS (N=61)</td>
<td>Evaluable Set (N=24)</td>
</tr>
<tr>
<td>Subjects with a ROP Examination</td>
<td>47</td>
<td>22</td>
</tr>
<tr>
<td>Subjects with a Maximum Severity of ROP of: n (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Secondary Endpoints**

**Time to Discharge from Neonatal Intensive Care**

The difference in the TDNIC was not statistically different, 82 days vs 74 days (p=0.3736) for the FAS and 74 days vs 74 days for the Evaluable Set.

**Bronchopulmonary dysplasia**

In the FAS more than 85% of both the rhIGF-1/rhIGFBP-3 and Standard of Care groups had some degree of BPD and the difference in presence or absence of BPD between the 2 groups was not statistically significant (0.19%, 95% CI: -11.58, 11.21). However, the difference in the distribution of severe BPD between the 2 groups was statistically significant (p=0.0380), with half the percentage of severe BPD seen in the rhIGF-1/rhIGFBP-3 group compared to the Standard of Care group (21.28% vs 44.90%). This was confirmed in the Evaluable Set (p=0.0169), where the percentage of severe BPD in the rhIGF-1/rhIGFBP-3 group was 4.76%, compared to 44.90% in the Standard of Care group.

**Intraventricular hemorrhage**

In the FAS the percentage of subjects with IVH greater than Grade 1 was smaller in the rhIGF-1/rhIGFBP-3 group than in the Standard of Care group (19.67% vs 30.0%), although this difference was not statistically significant (-10.33%; 95% CI: -25.62, 4.97). Subjects in the rhIGF-1/rhIGFBP-3 group had less severe IVH (3.3% vs 8.3% for Grade IV and 9.8% vs 15% for Grade III). The difference was more dramatic in the Evaluable Set where no subjects in the rhIGF-1/rhIGFBP-3 group had severe IVH, while 8.3% in the Standard of Care group did.
Growth parameters

There was no difference between the rhIGF-1/rhIGFBP-3 and the Standard of Care group in the rate of growth in weight, height or head circumference.

Per agreement with the [redacted], efficacy analyses would be performed excluding the data from 3 subjects at Site [redacted] (1 subject randomized to rhIGF-1/rhIGFBP-3, and 2 subjects randomized to standard neonatal care). Analyses of maximum severity of ROP across all examinations by a centralized pediatric ophthalmologist, severity of BPD, rate of growth (height, weight and head circumference), and presence of IVH were repeated on data of 60 subjects in the rhIGF-1/rhIGFBP-3 group and 58 subjects in the Standard of Care group. The conclusions using data from the FAS were not altered.

Safety results:

Deaths

There were a total of 19 deaths during the study, 12 deaths in the rhIGF-1/rhIGFBP-3 group and 7 deaths in the Standard of Care group. The imbalance in the number of deaths is concentrated in the <26 Weeks GA subgroup and driven by 3 more cases of NEC, one iatrogenic death due to a misplaced umbilical catheter and one infant with severe respiratory distress with onset prior to study drug infusion.

<table>
<thead>
<tr>
<th>Number of Deaths in Section D</th>
<th>rhIGF-1/rhIGFBP-3</th>
<th>Standard of Care</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>&lt;26 Weeks GA</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>≥26 Weeks G</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
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</table>

Serious adverse events

Forty-eight (78.7%) subjects in the rhIGF-1/rhIGFBP-3 group had a total of 105 SAEs. No subject had a SAE considered to be related to the study drug. Thirty-seven (61.7%) subjects in the Standard of Care group had a total of 101 SAEs. The SOC with the most rhIGF-1/rhIGFBP-3 subjects with SAEs were Infections and infestations (rhIGF-1/rhIGFBP-3 group: 19 subjects, 31.1%; Standard of Care group: 14 subjects, 23.3%). The SOC with the most Standard of Care subjects with SAEs was Respiratory, thoracic, and mediastinal disorders (rhIGF-1/rhIGFBP-3 group: 16 subjects, 26.2%; Standard of Care group: 19 subjects 31.7%).

Discontinuations due to adverse events

Twenty subjects discontinued as a result of a treatment-emergent AE, including 11 subjects in the rhIGF-1/rhIGFBP-3 group and 9 subjects in the Standard of Care group. All 11 subjects in the rhIGF-1/rhIGFBP-3 discontinued due to AEs with a fatal outcome; a twelfth subject in this group had a SAE with a fatal outcome but the parents withdrew consent to participate in the study prior to the subject’s death and withdrawal rather than death is the reason recorded for the discontinuation. Seven of the 9 subjects in the Standard of Care group discontinued due to SAEs with fatal outcomes; of the remaining 2 subjects, 1 subject discontinued due to a severe SAE of intestinal perforation that resolved and the second discontinued due to a severe SAE of...
Name of sponsor/company: Premacure AB, A Member of the Shire Group of Companies

Name of finished product: Mecasermin rinfabate

Name of active ingredient: rhIGF-1/rhIGFBP-3

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<th>volvulus that resolved with sequelae.</th>
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**Treatment-emergent adverse events**

The most frequent TEAEs, those occurring in 50% or more of subjects in either group include patent ductus arteriosus (rhIGF-1/rhIGFBP-3: 55 subjects, 90.2%; Standard of Care: 51 subjects 85.0%), bronchopulmonary dysplasia (rhIGF-1/rhIGFBP-3: 34 subjects, 55.7%; Standard of Care: 38 subjects (63.3%), neonatal respiratory distress syndrome (rhIGF-1/rhIGFBP-3: 29 subjects, 47.5%; Standard of Care: 34 subjects, 56.7%), neonatal anemia (rhIGF-1/rhIGFBP-3: 46 subjects, 75.4%; Standard of Care: 44 subjects 73.3%), retinopathy of prematurity: (rhIGF-1/rhIGFBP-3: 39 subjects, 63.9%; Standard of Care: 37 subjects, 61.7%), and neonatal jaundice (rhIGF-1/rhIGFBP-3: 28 subjects, 45.9%; Standard of Care: 30 subjects, 50.0%).

**Safety laboratory parameters**

There were no notable differences between the groups in clinical chemistry, hematology, or blood gas laboratory parameters.

The percentage of subjects with blood glucose concentration that met the study definition of hypoglycemia (<2.5 mmol/L) was 26.2% for the rhIGF-1/rhIGFBP-3 group and 31.7% for the Standard of Care group.

No subjects administered rhIGF-1/rhIGFBP-3 were positive for anti-IGF-1/IGFBP-3 IgG and IgM antibodies.

**Other safety parameters**

There were no differences in reports of cardiac hypertrophies between the 2 groups and there were no events of tonsillar hypertrophy or intracranial hypertension.

**Conclusions:**

ROPP-2008-01 did not meet the primary endpoint in reducing severity of retinopathy of prematurity (ROP). However, strong positive trends were observed in secondary endpoints related to bronchopulmonary dysplasia and intraventricular hemorrhage. There were no newly identified risks and no important changes to the previous knowledge of safety for SHP607, rhIGF-1/rhIGFBP-3, that would impact the risk benefit profile. The current dose of 250 µg/kg/24 hours aimed for the lower bound of the target normal intrauterine range and few serum samples had IGF-1 levels that exceeded the range. Overall, the results of ROPP-2008-01 support the continued evaluation of rhIGF-/rhIGFBP-3 for the treatment of complications of premature birth at both the current dose and a higher dose.

**Date of report:** 18 Nov 2016