FRONT PAGE

PROJECT FINAL REPORT

4.1 Final publishable summary report (max 40 pages)

The text is organized in 5 textboxes to be completed in Participant Portal

Textbox 1 Executive summary (max 1 page)

Retinopathy of prematurity (ROP) is a rare disease according to International Rare Diseases Research Consortium (IRDiRC) classification. ROP is a major cause of blindness in children in the developed and developing world, despite current treatment of late-stage ROP. As developing countries provide more neonatal intensive care, the incidence of ROP is increasing as more preterm children are saved. Approximately 40% of perinatal blindness can be attributed to ROP.

The treatment of ROP, ablation of the avascular retina with laser photocoagulation or cryotherapy to cause involution of pathological vessels, has remained fundamentally unchanged for almost 50 years. These treatments are destructive and destroy the peripheral (non-vascularised) parts of the retina and may lead to a partial loss of peripheral or side vision.

In the PREVENT-ROP project, we aimed to develop a novel, non-destructive, vessel protective,

treatment in order to promote normal vessel development in infants born extremely preterm.

The PREVENTROP project is a six-year FP7-funded project designed to perform clinical trial evaluating impact of a new growth factor treatment in extremely preterm infants. In the project ten partners from universities and industries from Sweden, Germany, Great Britain, the Netherlands, Italy and Norway and the USA worked together.

We have secured drug manufacturing and performed a phase II clinical trial on impact of this new treatment on ROP development and other neonatal morbidities. Based on the results of the phase II trial we have developed a phase IIb multi-centre (world-wide) study protocol, which has been discussed with EMA/FDA. The recruitment of study sites has been completed and the phase IIb study is set to start March 2019. In addition, we have successfully developed experimental models and specific point-of-care test to support the design of the phase III clinical trial.

Textbox 2 Summary description of project context and objectives (max 4 pages)

Background and Objectives

The overall objective of the PREVENTROP project is to develop a novel preventative intervention for the blinding disease ROP and other complications of prematurity. This work is based on the concept that replacement of critical factor(s), normally provided in utero and reduced due to the disruption of the maternal/fetal interaction, to the infant born prematurely will help prevent the complications of premature birth.

It has been shown experimentally and clinically that low levels of the growth factor Insulin-like growth factor 1 (IGF-I) in premature infants strongly correlate with ROP development, indicating that IGF-I is one of these critical factors. Our preliminary work suggests that replacement of IGF-I to normal levels found in utero will prevent ROP and other complications of premature birth

The PREVENTROP consortium proposes during the project period to conduct preclinical studies in mice model of ROP and rabbit pup models to refine the clinical approach. In addition we will conduct clinical studies: pharmacologic, pharmacodynamic, pharmacokinetic and toxicologic including phase II and phase III clinical trial of an EU designated orphan medicinal product IGF-I/IGFBP-3 complex to address treatment for ROP and other serious complications in premature infants.

Primary Objectives in the phase I-II study

- To determine the dose of rhIGF-I/rhIGFBP-3, administered by continuous intravenous 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 (30-100 µg/L), in premature infants.
- To determine serum levels of IGF-I and associated pharmacokinetic parameters after continuous intravenous infusion of rhIGF-I/rhIGFBP-3.

Secondary Objectives in the phase I- II study

- Follow up of safety and efficacy parameters
- Primary objective of the phase II- study
- To compare the severity of retinopathy of prematurity among treated infants with untreated control patients, matched for GA at birth and gender.

Secondary objective of the phase II study

- Development of a) bronchopulmonary dysplasia (BPD); b)intraventricular haemorrhage (IVH); c); d) body weight; e) length; f) head circumference; g) brain development; h) cognitive outcome and i) total number of days in neonatal intensive care prior to discharge.
- Conduct translational studies for the understanding of variation in infant response to treatment and will be undertaken in appropriate mouse model of retinopathy and preterm rabbit pup models and in in-vitro systems.

We believe that multidisciplinary networks like PREVENTROP collaboration provides the infrastructure that is necessary for performance of clinical trials and subsequent monitoring of newly authorized products.

Public website: **www.preventrop.gu.se**

The proposed project has a very different approach to interventions for ROP than those currently applied. Instead of late stage treatment of sight threatening ROP, our research focuses on how to improve care during the first few weeks of life to promote growth of vascular and neural tissues in the retina thus avoiding the development of a large avascular zone and subsequent abnormal vessel growth.

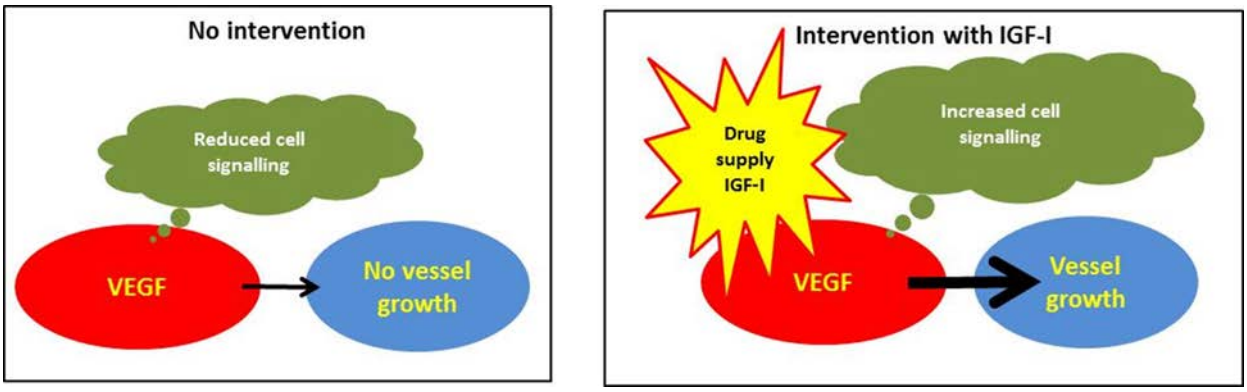

Figure 1: Absence of IGF-I (left), preventive treatment with IGF-I (right)

In the absence of sufficient IGF-I there will be impaired cell signalling for the action of VEGF (Vascular Endothelial Growth Factor, today's state of the art), with the expected progress beyond state of the art the preventative treatment with IGF-I will allow cell signalling for VEGF action to allow normal vessel growth Figure 1.

The objectives for the project are listed in Table 1.

Table 1: Objectives for the project

No	Objectives
1	Establish the role of IGF-I by clinical trial (phase II).
2	Development of POC test equipment for safe and fast analyse of IGF-I in blood serum.
3	Supply of a new IGF-based drug (Premiplex®) for clinical trials, phase II and phase III.
4	Establish the role of IGF-I by preclinical studies in mice and rabbits models.
5	Prepare a protocol for clinical trial (phase III).
7	Prepare for marketing of Premiplex®.

Clinical trial

The new clinical is aimed to determine if the investigational drug (SHP607) can reduce respiratory complications in extremely premature babies through 12 months corrected age (CA), as compared to extremely premature babies receiving standard neonatal care alone.

Arms and Interventions

	Intervention/treatment
Experimental: SHP607 250 mcg/kg/24 hours Participants will receive SHP607 at a dose of 250 microgram (mcg)/kg/24 hours through continuous intravenous (IV) infusion from birth up to postmenstrual age (PMA) 29 weeks +6 days.	Drug: SHP607 Intravenous infusion of SHP607 at doses of 250 mcg/kg/24 hours and 400 mcg/kg/24 hours from birth up to PMA 29 weeks + 6 days. Other Name: Mecasermin Rinfabate
Experimental: SHP607 400 mcg/kg/24 hours Participants will receive SHP607 at a dose of 400 mcg/kg/24 hours through continuous IV infusion from birth up to PMA 29 weeks +6 days.	Drug: SHP607 Intravenous infusion of SHP607 at doses of 250 mcg/kg/24 hours and 400 mcg/kg/24 hours from birth up to PMA 29 weeks + 6 days. Other Name: Mecasermin Rinfabate
No Intervention: Standard Neonatal Care Neonatal care alone will be provided.	

Primary Outcome Measures: To assess the effect of SHP607 on reducing the burden of chronic lung disease (CLD), as indicated by a reduction in time to final weaning off respiratory technology support (RTS)through 12 months corrected age (CA), as compared to a standard neonatal care group.

Secondary Outcome Measures:

1. Incidence of Bronchopulmonary Dysplasia (BPD) at Postmenstrual Age (PMA) 36 Weeks [Time Frame: PMA Week 36]
2. Incidence of intraventricular hemorrhage (IVH) through PMA 40 weeks, as assessed by cranial ultrasound. [Time Frame: Baseline Through PMA 40 Weeks]
3. Functional Status as Assessed by PREMature Infant Index (PREMII) at Postmenstrual Age (PMA) 40 Weeks [Time Frame: PMA Week 36]
4. Incidence of Retinopathy of Prematurity (ROP) [Time Frame: PMA Week 31 up to Week 40]

Main results

A description of the work performed since the beginning of the project and the main results achieved so far:

Resulting pharmacokinetic and safety data were published and reported to the Swedish Medical

Product Agency (MPA), and formed the basis for continued study Phase II. In a continued Phase II study of infants born at 23-28 GW, infants received treatment until endogenous production of IGF-1 was considered sufficient (median duration 21 days) and matched individuals were evaluated as controls. The multi-center expansion required simplification of the infusion protocol; this was achieved by developing a population PK model which predicted that physiologic replacement could be achieved with a uniform dose. Phase II study was expanded to a European multi-center study, which was finalized in 2015. Results were launched June 2016 and planning was ongoing for The Phase III study. Meetings with regulatory bodies (FDA and EMA) has been undertaken and based on these meetings a protocol for Phase IIb has been being finalised. Start of the Phase IIb trial is planned for Q1 2019.

Parallel to the clinical studies intensified work securing drug manufacturing for the clinical phase III study has been successful. For instance, technology rights for drug manufacturing have been transferred from the company Insmed (USA) to one of the partners. Also full scale GMP drug substance for the Phase 3 trial has been manufactured.

Textbox 3 Description of main S &T results/foregrounds

(max 25 pages)

The project aimed to develop a drug PREMIPLEX® and perform a clinical trial with the drug evaluation impact on ROP development.

The main achievements in the reported periods are described below.

In WP2, WP3, WP5 and WP6 the project was focusing on the development of a POC-test for monitoring infants on treatment, fabrication of the drug, performing a phase 2 trial, designing and performing a phase III trial.

The achieved results in the period are:

- A Phase 2 clinical trial have been performed. (WP1)

- The POC-test has been developed (WP2)

- Drug manufacturing for mass production has been secured (WP3).

- The two animal models of relevance for the project have been developed (WP4).

- A study protocol for the phase III study have den developed (WP5).

- Recruitment of sites to perform the phase III study has been finalized (WP6).

WP7 includes the activities in dissemination, exploitation and standardization. The achieved results are:

- The results from the project have been published and presented at conferences, on homepages and at www.clinicaltrial,gov for wider audience (end-users and authorities).

The results from the WPs are described in the followings:

WP1 Clinical trial, phase II

***Objectives**:*

– Scientific coordination and meetings

– To complete a clinical trial, phase II study – with emphasis on pharmacokinetics and pharmacodynamics, safety and efficacy evaluation.

Primary Objectives in the proposed phase II study

- To determine the dose of rhIGF-I/rhIGFBP-3, administered by continuous intravenous 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 premature infants.
- To determine serum levels of IGF-I and associated pharmacokinetic parameters after continuous intravenous infusion of rhIGF-I/rhIGFBP-3.

Secondary Objectives in the proposed phase II study

- Follow up of safety and efficacy parameters

Results:

- The Phase II study expanded to a European multi-center study, being finalized in 2016. The multi-center expansion required simplification of the infusion protocol; this was achieved by developing a population PK model which predicted that physiologic replacement could be achieved with a uniform dose, 250 microgram/kg/24h of the IGF-1/IGFBP-3 complex.
- Training of hospital personnel (EU and USA) was performed
- The phase II trial was finalised in March 2016
- Data collection and management for Phase II trial was finalised in September 2016
- Statistical analyses for the Phase II trial was finalised in November 2016.
- Preparation of study report to MPA was finalised in January 2017

WP2 Development of POC test

Objectives:

-The task is to develop a POC test system for rapid quantification of IGF-I from blood samples in the high sensitivity range. The currently used system, Mediagnost ELISA E20, is a non extractive sandwich immunoassay test using serum or plasma that fulfils the distinct requirement for high sensitivity. However, it needs laboratory work and equipment, and time to result is with several hours longer than needed.

MEDI will develop a rapid and secure IGF-I-POC analysis for optimal monitoring regime.

Results:

- The POC-test for measuring IGF-1 in concentration range of 20 -200ng/mL within 20 minutes

- usability of the test system was evaluated in clinical settings of three university hospitals

- a third party validation of the test system was conducted by a Shire CRO and fulfillment of the requirements for usage in clinical trials is proven

- assay comparison with radioimmunoassay revealed reasonable correlation of assay results

- production processes were established

WP3 Drug manufacturing and authorization

Objectives:

To ensure that current standards for GLP, GMP and GCP are met to qualify for market authorization in EU (authorization agency EMA) and USA (authorization agency FDA).

Results:

- Drug product manufacturing to support the Phase 2b trial has been performed
- Fujifilm Diosynth has been selected for drug substance development, testing and manufacturing
- Technology Transfer package has been prepared by Insmed Inc.
- Full scale GMP drug substance for the Phase 3 trial has been manufactured.
- From discussions with EMA and FDA it appear that drug authorization cannot be finalized as planned in the project period.
- As more pre-clinical and clinical data will be required for a successful ODD application, Shire plans to submit the application, once more data becomes available but potential timelines for submission have not yet been established.

WP4 Preclinical and basic research

Objectives:

- Conduct preclinical research studies to establish mechanisms for clinical findings in phase II-III.
- Bridge clinical findings and pathogenic mechanisms to define variation in infant response to treatment.
- Evaluate clinically observed or hypothesized interactions between study drug treatment (IGF-I/IGFBP-3), normal preterm postnatal physiological adaptation and specific entities of clinically occurring morbidity.

These translational studies will be essential for the understanding of variation in infant response to treatment and will be undertaken in appropriate mouse model of retinopathy and preterm rabbit pup models and in in-vitro systems.

Results:

- Two translational animal models have been developed within the project.

- One mouse model for analyzing metabolic impact on ROP development, that has provided pathogenetic mechanisms of IGF-I on angiogenesis.

- One rabbit model for studying brain development and injury after preterm birth,that has provided pathogenetic mechanisms of IGF-I on neurogenesis.

WP5 Design of clinical trial, phase III

Objectives:

In order to achieve market authorisation of the orphan designated drug Premiplex® a phase III study has to be conducted. The objective is therefore to implement a phase III study in order to bring this preventative drug to the market. Based on these meetings with regulatory authorities

(FDA and EMA) a protocol for Phase IIb proceeding a Phase III is being finalised. Start of the Phase IIb trial is planned for Q1 2019.

Results:

- Phase IIb Study protocol was finalised in Q3 2018.

WP6 Clinical trial, phase III

Objectives:

The overall objective of the phase III clinical trial was to investigate the safety and efficacy of the orphan drug Premiplex® as a preventative treatment initially for ROP. Based on the results in the Phase II and with meeting with regulatory bodies the objective has shifted to investigate the safety and efficacy on chronic lung disease.

The results from the project are used in this future project carried out by Shire.

The objective of the Shire project is to in a Phase IIb investigate safety and efficacy of the orphan drug Premiplex® as a preventative treatment for chronic lung disease. With the secondary objectives; b) Intraventricular haemmorhage; c) metabolic state; d) body weight; e) length; f) head circumference; g) brain development; h) cognitive outcome and i) PREMII.

Primary objective of the future Shire project:

- The primary objective of this study is to assess the effect of SHP607 on reducing the burden of chronic lung disease (CLD), as indicated by a reduction in time to final weaning off respiratory technology support (RTS) through 12 months corrected age (CA), as compared to a standard neonatal care group.

Secondary objectives of the future Shire project:

- To assess the effect of SHP607, as compared to a standard neonatal care group, on:
- • Chronic respiratory morbidity
- o Incidence of bronchopulmonary dysplasia (BPD) at postmenstrual age (PMA) 36 weeks, defined by need for oxygen or respiratory support, or death.
- o Total number of days on RTS from birth through 12 months CA
- o Duration (length of stay) of rehospitalizations due to respiratory diagnoses through 12 months CA.
- o Number of emergency room visits associated with a respiratory diagnosis through 12 months CA.
- o Number of days of respiratory medication use (eg, bronchodilators, steroids, leukotriene inhibitors, diuretics) through 12 months CA.
- o Incidence of signs and symptoms of respiratory disease at 12 months CA as assessed by a 28-day caregiveradministered diary.
- o Incidence of chronic respiratory morbidity (CRM1) through 12 months CA.
- o Incidence of chronic respiratory morbidity including symptoms of respiratory disease (CRM2) through 12 months CA.

- o Severity of chronic respiratory morbidity as indicated by a CLD of infancy severity score (CRM3) through 12 months CA.
- • Neurologic outcomes
- o Incidence of intraventricular hemorrhage (IVH) through PMA 40 weeks, as assessed by cranial ultrasound.
- o Motor function at 12 months CA, as measured by Alberta Infant Motor Scales (AIMS).
- • The PREMature Infant Index (PREMII) at PMA 36 weeks, a Clinician-Reported Outcome (ClinRO) assessment of functional status.
- • Incidence of retinopathy of prematurity (ROP)
- • Mortality from birth through 12 months CA
- • Exposure-response pharmacokinetic/pharmacodynamic (PK/PD) relationships between IGF-1 exposure and respiratory and neurologic endpoints to support Phase 3 dose selection

Additional objectives:

To assess the effect of SHP607, as compared to a standard neonatal care group, on:

- • Quality of life measures
- o Caregiver health status using EuroQol 5-dimensional 5-level descriptive system (EQ-5D-5L)
- o Subjects' health-related quality of life (HRQoL) using the Pediatric Quality of Life Inventory (PedsQL™) Infant Scales

Results:

- Site selection and initiations are ongoing

- The future Shire project will start Q1 2019.
- Training of hospital personnel (EU,USA, Asia) has been initiated.

WP7 Dissemination and exploitation

Objectives:

- Through publications and conference participation ensure efficient dissemination and exploitation of the new knowledge on the preventative treatment with IGF-I. The target groups are relevant clinicians, scientists and policymakers. Dissemination will take place during the whole project period.
- Input from discussions in relation to conference presentations and publications of manuscripts has been combined with the findings from the study in suggestions for a European guideline for treatment with Premiplex® in neonatal care settings.

Exploitation will take place during the project period and after the end of the project. To ensure rapid implementation of the new knowledge a final PREVENTROP conference has been organized in September 2018 with invited industry experts.

Results:

- Both the project and results from the studies within the project have been presented in numerous publications and at presentations at conferences.

WP8 Management

Objectives:

Establish tools and procedures for high quality in project management to ensure that the objectives are fulfilled within budget and time.

Results:

Project Management includes 1) Scientific management which is carried out by in scientific WPs (WP1-WP7) and 2) Project administration which is carried out in WP8.

Scientific management is carried out by the coordinator UGOT. The scientific management team includes:

- Professor Ann Hellström, Head of SCPO (The Sahlgrenska Center for Pediatric Ophthalmology)
- Associate professor Chatarina Löfqvist, PhD, SCPO

Scientific management is carried out in close collaboration with the WP-leaders.

Two-day Consortium meetings are organized every 6 month with participation of the whole consortium (2-4 participants from each of the 10 partners).

Scientific progress at WP-level has been discussed in details at each of the partner meetings and six-month plans for the following period have been prepared by each partner.

The scientific progress have been continuously monitored and followed up by adjustments as necessary. In summary, scientific management has been very efficient and timely.

Project administration is carried out by UGOT. The project administration team includes

- Fundraiser Anders Bjerrum, SCPO
- Tinna Carlsson, Financial officer, Central EU-office at UGOT
- Henrik Lindskog, Research advisor, Central EU-office at UGOT

The work includes:

- Administration of the intranet for sharing documents between partners
- Collection of six-month financial Reports from partners
- Participation in the six-month partner meeting and presentation of financial status
- Periodic reporting to EC (scientific and financial)

Textbox 4 Potential impact and main dissemination activities and exploitation results (max 10 pages)

A challenge for the European Society is the increasing number of surviving preterm infants with long-term morbidities. Our project have focused on research on preventative diagnostics and treatment for this cohort.

The project when finalized has the potential to achieve system-wide improvements in health outcomes in extremely preterm infants. With new preventative treatment and new monitoring POC-test will help reduce severe morbidities, hospital stay and in the long-term reduce cost of disability calculated as Disability-Adjusted Life Year (DALY).

It has been estimated[1] that the absolute costs attributable to preterm birth rise steeply at very low gestations. They estimate a decreasing average cost per surviving infants born at week 23 ranging from 380.000 Euros/infant to 120.000 Euros/infant born at week 25 after which costs very slowly decrease with increasing gestational age at birth. These costs are primarily attributable to neonatal intensive care due to prolonged hospital stay in survivors, discharge being at around 40 weeks postmenstrual age, giving an average of 4 months care for the most immature.

MEDI will market the POC test equipment FAST-IGF1 to health care providers, NICUs, neonatologists, clinicians and physicians worldwide. MEDI will provide single tests (depending on the useful for rapid bedside testing and enabling quantification of biomarkers by a handhold device. The potential market for one such biomarker test is assessed from the 500.000 European preterm babies per year[2]. Assuming an acceptance of 50% and 3 measurements per patient during monitoring, a calculated market potential of 0.75 million tests per year in Europe, and consequential approx. 2.5 million tests per year worldwide can be expected as the end point. Depending on the number of finally identified applicable biomarkers the potential number of tests per year has to be multiplied respectively. The estimated selling price ranges from minimal 10 up to 50 Euro per test. Within the first 5 years after successful end of the project, and the test IVD approval provided, one can expect an additional respective annual turnover of approx. 10 million Euro, with several new jobs at MEDI.

SHIRE will provide data on efficacy and long-term ocular outcomes over the first 5 years of life in extremely prematurely born infants treated with rhIGF-1/rhIGFBP3 versus standard of care. Impact of IGF-1 therapy (product) on key comorbidities of prematurity (chronic lung disease and neurodevelopmental disabilities) will also be captured as will total resource utilization required for the care of these children. (Figure. 2)

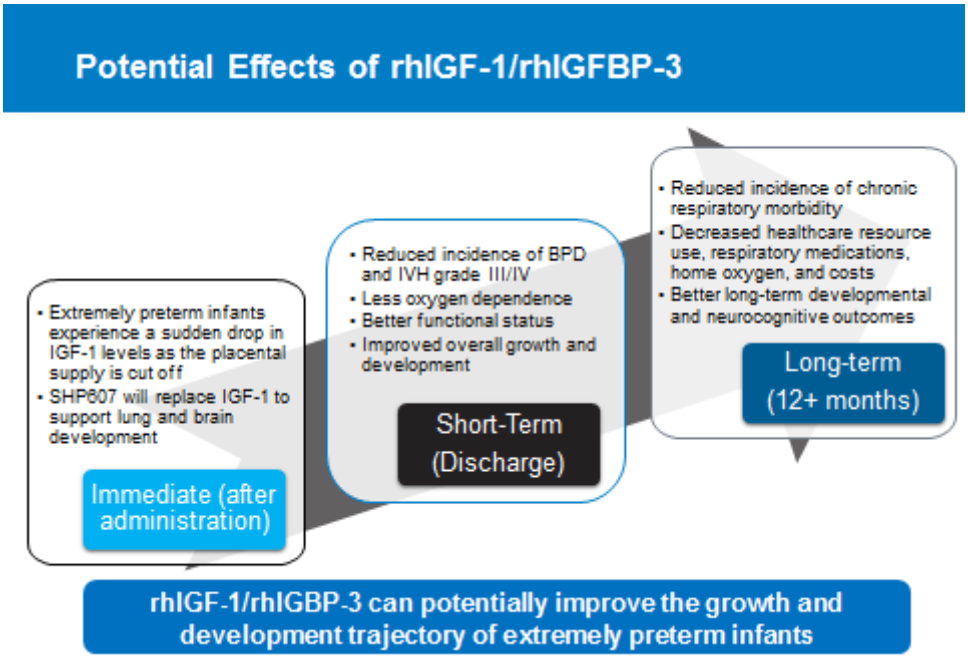

Figure 2: Overview of potential preventative effects of rhIGF-I/rhIGFBP-3 replacement to normal levels found in utero.

[1] Chang et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet. 2013 Jan 19;381(9862):223-34.

The product will, if ongoing clinical trial is successful, be launched in Europe and North America at earliest in 2024 and is anticipated to benefit approximately 20-25,000 infants in each of these markets. To support these activities in Europe, approximately 100 new jobs will be created in Research and Development, Manufacturing and Product Distribution, and Sales, Marketing and Product Support. The distribution channel for this orphan drug product is via traditional hospital formularies with neonatologist and neonatal intensive care units as the end-users.

SMERs motivation for participating in the PreventROP project was to provide CRO services in the project and later in clinical research performed by the consortium members. Through this project, SMER has expanded its competence in the rapidly developing area of clinical research within NICU/neonatology. This competence will help SMER to position the company as a preferred CRO for small and medium sized companies in this clinical niche with a dedicated speciality service unit for NICU clinical trials. Several new projects are now being planned, and SMER is actively pursuing commercial (CRO) opportunities in the neonatology sector. This project has further helped facilitate the planned opening of SMER subsidiaries in other countries such as Italy, the Netherlands and the US.

In view of the growing number of preterm infants, the risks and possible life-long consequences of preterm birth for the infant, their family and society, it is clear that prematurity poses a serious and growing threat. In recent years, the European Union's political and health care institutions have recognized the importance of addressing the health of the most vulnerable group of all – our prematurely born children "Too little –too late?"[2].

In Europe about 500.000 babies are born *preterm* every year[3]; these infants represent Europe´s largest paediatric patient group. *Preterm birth* is today the leading cause of long-term neurological disabilities in children in the EU and worldwide[4]. In most countries with reliable data, preterm birth rates remain constant or are increasing. This coupled with the fact that survival rates of premature infants have increased dramatically over the last decades[5] leads to increasing numbers in this group of future European citizens. More than 50% of the infants born with a gestational age <28 weeks will suffer some long-term neurologic impairment if they survive the neonatal period[6]. Many specific complications (i.e. morbidities) after p*reterm birth* are, associated with immaturity including the sight-

[2] Haumont et al. The situation and the challenges with regard to preterm birth in Europe. European Foundation for the Care of Newborn Infants http://www.ecswe.net/wp-content/uploads/2013/04/QOC4-Chapter-2.pdf

[3] Europeristat Report 2010 - http://www.europeristat.com/reports/european-perinatal-health-report-2010.html

[4] Blencowe et al. Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study. *Pediatric Research* (2013) 74, 4–16

[5] Blencowe et al National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379: 2162–2172.

[6] Blencowe et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels 2010. Ped. research 2010 74(Suppl1) S2

threatening disease ROP, intracranial haemorrhage and respiratory problems[7] which were all addressed in the PREVENROP project.

In 2010, there were an estimated 13 million preterm infants who survived beyond the first month. In preterm infants born with a gestational age less than 28 weeks, over half (52%) are estimated to have some long-term impairment. This means that 345.000 were estimated to have moderate or severe neurodevelopmental impairment, and a further 567.000 were estimated to have mild neurodevelopmental impairment. Many more have specific learning or behavioural impairments or reduced physical or mental health.

Textbox 5 Address of project public website and relevant contact details

https://preventrop.gu.se/

End of 4.1 Final publishable summary report (max 40 pages)

[7].EXPRESS Group. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA. 2009 Jun 3;301(21):2225-33.