

Test drug (IMP) and Pharmaceutical Company	SMOFLipid® Fresenius Kabi AG, Bad Homburg, Germany
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CLINICAL STUDY PROTOCOL

PREVENTING CHOLESTASIS IN PREMATURE INFANTS USING SMOFLIPID®

Version 1.~~21~~ / ~~9.3.2012~~ 17.9.2012

Confidentiality Statement

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Protocol authors	Andreas Repa, MD
Investigators	Andreas Repa, MD Nadja Haiden, MD Renate Fuiko, PhD
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1. SPONSOR, INVESTIGATOR, MONITOR AND SIGNATURES

Sponsor/or representative (OEL) (AMG §§ 2a, 31,32)

Medical University of Vienna, Austria
O. Univ. Prof. Dr. Arnold Pollak

Signature (OEL)

Date

Investigator (AMG §§ 2a, 35,36)

PD Dr. med. univ. Nadja Haiden, Department of Pediatrics, Medical University of Vienna, Austria

Signature

Date

Monitor/ or Representative of CRO (AMG §§ 2a, 33,34)

Koordinierungszentrum für Klinische Studien
(PD.Dr. Johannes Pleiner)

Signature

Date

Statistician

Mag. Irene Steiner

Signature

Date

Clinical Trials Centers:

Medicial University of Vienna, Austria

2. PROTOCOL SYNOPSIS

TITLE	Preventing Cholestasis in Premature Infants Using SMOFLipid®					
OBJECTIVES	<p>Primary Objective</p> <ul style="list-style-type: none"> To compare a mixed parenteral lipid emulsion containing fish oil (SMOFLipid®) with a soybean oil based lipid emulsion (Intralipid®) for its effect on the occurrence of parenteral nutrition associated cholestasis in extremely low birth weight infants <p>Secondary Objectives</p> <ul style="list-style-type: none"> To assess the impact of SMOFLipid® on the long term neurocognitive development of extreme low birth weight infants at 12 and 24 months of corrected age 					
DESIGN / PHASE	Prospective, randomized, double-blind, phase IV study.					
STUDY PLANNED DURATION	First patient First visit	1st month	Last patient First visit	36 month s	Last patient Last visit	62 months
CENTER(S) / COUNTRY(IES)	Single center, Austria (Medical University Vienna, Austria; Department of Neonatology, Pediatric Intensive Care and Neuropediatrics, University Children's Hospital,)					
PATIENTS / GROUPS	<p>200 patients in 2 groups 100 patients per group Block randomization ratio 1:1, stratification by sex and weight (in two groups: < 750 gram vs. ≥750 gram).</p> <p>In case of twins, randomization will be applied to the firstborn; the twin will be assigned to the other treatment group. Triplets or higher will be excluded.</p>					
INCLUSION CRITERIA	<ul style="list-style-type: none"> Infants born with a birth weight ≤ 1000 Gram (= extreme low birth weight infants) Admission to the neonatal ward in the first 24 hours of life Informed consent obtained and randomized on study drug the first 5 days of life 					
EXCLUSION CRITERIA	<ul style="list-style-type: none"> Triplets or higher Conjugated bilirubin > 1.5 mg/dl before inclusion to the study Conditions associated with cholestasis independent of parenteral nutrition: <ul style="list-style-type: none"> Inborn errors of metabolism Viral Infections (cytomegaly virus, HIV, Hepatitis B, C) Immune mediated hemolytic disease (e.g. Rhesus incompatibility) Cystic fibrosis Primary cholestatic diseases of the liver For Neurodevelopmental outcome in follow up phase: Congenital neurological malformations 					
STUDY PERIODS	<ul style="list-style-type: none"> Operational Phase: The operational phase of the study will last for three years (months 1-39) and start with the inclusion of the first patient to the trial and will end with the last patient's discharge from hospital. Follow Up: The follow up phase will last start with the first included patient reaching the age of 12 months corrected age and will end at 24 months of corrected gestational age of the last included patient (months 15-62) 					
INVESTIGATIONAL DRUG	SMOFLIPID®:					

	initial dose: 1g/kg/day target dose: 3g/kg/day
COMPARATIVE DRUG /CONTROL CONDITION	INTRALIPID® initial dose: 1g/kg/day target dose: 3g/kg/day
CONCOMITANT MEDICATION	In case of of cholestasis (i.e. conjugated bilirubin two times > 1.5 mg/dl), ursodeoxycolic acid at 20-30 mg/kg/day is the treatment of choice. In case of severe cholestasis (i.e. conjugated bilirubin > 6 mg/dL) and elevation of liver enzymes (3 times over normal) a rescue therapy using pure fish oil (Omegaven®) at 0.5-1 g/kg/day will be allowed.
EFFICACY ENDPOINT	Incidence of parenteral nutrition associated cholestasis (PNAC), defined as conjugated bilirubin > 1.5 mg/dl measured on two consecutive occasions by blood sampling performed at least every 10 +/- 4 days. Based on a present incidence of 25 % using the comparative drug at the study center (unpublished data 2007-9) an absolute difference of 15 % between the groups (25% vs. 10% incidence) was considered clinically significant.
TOLERABILITY / SAFETY ENDPOINTS	-
PHARMACOKINETIC / PHARMACODYNAMIC ENDPOINTS	-
QUALITY OF LIFE / PHARMACOECONOMIC ENDPOINTS	-
STATISTICAL METHODOLOGY	<p>Primary Endpoint PNAC (definition see efficacy endpoint)</p> <p>Null and alternative hypotheses: <i>H₀ : The percentage of PNAC in group 1 (investigational drug) equals group 2 (comparative drug)</i> <i>H₁: The percentage of PNAC in group 1 (investigational drug) does not equal group 2 (comparative drug)</i></p> <p>Sample size calculation A sample size estimation using a χ^2-test indicated that 200 infants (100/group) are required to detect a 15% difference (10% in group 1 vs. 25% in group 2) with a power of 80% and a two-sided significance level of 0.05. The estimated drop out rate is 22%. Therefore, a sample size of 122 patients per group is planned. For sample size estimation, data were assumed to be independent.</p> <p>Statistical methodology Main analysis set(s) A χ^2-test will be used for analysis of the primary outcome PNAC. Additionally, the effect of treatment and other relevant influence factors (i. e. duration of parenteral nutrition, birth weight, necrotizing enterocolitis) on the primary endpoint will be analyzed using a logistic regression model with</p>

	<p>stepwise selection. In case of twins, the analysis will be carried out 1) as mentioned above, but only including the firstborn and 2) by calculating a generalized linear model with mother as random factor.</p> <p>Other endpoints</p> <p>Bailey Scales of Infant Development II at 12 and 24 months: Differences in the scores of psychomotor development and neurocognitive development, respectively, between the groups will be analyzed by repeated measures ANOVAs, also accounting for confounder factors (e.g. birth weight, ...). In case of twins, the analysis will be carried out 1) as mention above, but only including the firstborn and 2) by calculating a mixed model with mother and child as random factor. In case of too many drop outs, descriptive statistics will be carried out.</p> <p>For Gross Motor function measurements at 12 and 24 months, descriptive statistics will be conducted.</p>
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3. LIST OF ABBREVIATIONS

ELBW	Extreme Low Birth Weight
ICH	International Conference on Harmonization
ILE	Intravenous Lipid Emulsion
GCP	Good Clinical Practice
DHA	Docosahexaenoic Acid
DOH	Declaration of Helsinki
LC-PUFA	Long Chain Polyunsaturated Fatty Acids
PN	Parenteral Nutrition
PNAC	Parenteral Nutrition Associated Cholestasis

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TABLE 1. VISIT AND ASSESSMENT SCHEDULE

PERIODS	Name	SCREENING	TREATMENT									FOLLOW-UP
	Duration		months									2 years
VISITS	Number	1	2	3	4	5	6	7	8	9	10	11
	Name	Screening	Randomization	Control 1	Control 2	Control 3	Control 4	Control 5	Control 6	Control 7	End of Study	Follow-up
	Time	Day 0	Day 0-2	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 18	Month 16 and 28
				(± 4 days)	(± 4 days)	(± 4 days)	(± 4 days)	(± 5 days)	(± 7 days)	(± 7 month)	(± 1 month)	(± 5 days)
Informed Consent		X										
Inclusion / Exclusion Criteria		X										X
Medical History			X								X	X
Physical Examination			X								X	X
Body weight and height			X	X	X	X	X	X	X	X	X	X
Concomitant/Change in medication			X	X	X	X	X	X	X	X	X	
Vital Signs (BP, PR)			X	X	X	X	X	X	X	X	X	X
Lab Tests (Bilirubin, liver function)			X	X	X	X	X	X	X	X	X	
Visual evoked potentials											X {34-37wks} 36wks-GA}	
Cerebral Function Monitoring				X	X	X	X	X	X	X	X	
Cerebral Ultrasound			X	X	X	X	X	X	X	X	X	
Adverse Events (IVH, NEC, ROP, BPD)				X	X	X	X	X	X	X	X	
Psychomotor Developmental Tests												X
Ophtalmologic exam					X	X	X	X	X	X	X	X
Adverse Events				X	X	X	X	X	X	X	X	

5. BACKGROUND INFORMATION

5.1 Background

5.1.1 Parenteral nutrition associated cholestasis (PNAC)

Since the first description of parenteral nutrition associated liver disease ¹ it is well established that patients receiving parenteral nutrition (PN) are at risk for developing hepatic complications. In neonates and infants, liver injury is characterized by an early occurrence of intrahepatic cholestasis - i.e. parenteral nutrition associated cholestasis (PNAC) - characterized by a rise in serum conjugated bilirubin ². In severe cases liver cell damage and even progressive liver dysfunction with an incidence of hepatic failure of up to 17 % is described ³.

5.1.2. Extreme low birth weight infants

Preterm infants with extreme low birth weight (ELBW) < 1000 gram are often dependent on long term PN due to intolerance of enteral feedings ⁴. Additionally they frequently acquire nosocomial infections and are at risk for developing necrotizing enterocolitis, a severe inflammatory disease of the intestine with considerable long term morbidity such as short gut syndrome. Prematurity, long term PN, nosocomial infections, necrotizing enterocolitis and short gut syndrome are all risk factors for the development of PNAC. Therefore ELBW infants are at high risk to develop this complication ².

5.1.3. Parenteral lipids as pathogenic factor in PNAC

Besides factors related to prematurity and its complications or short gut syndrome, PNAC is - as already proposed by the condition's name - closely linked to aspects of PN. Hypercaloric feeds with an excess of glucose can result in chronic cholestasis ⁵. Most important however, intravenous lipid emulsions (ILE) seem to be implicated in the development of PNAC. Higher parenteral lipid administration has been documented to be correlated with cholestasis in pediatric patients ⁶ as well as very low birth weight infants ⁷.

5.1.4. Soybean oil based intravenous lipid emulsions

Until nowadays, standard of care for supplying lipids in PN of preterm infants and sick neonates are ILE based on soybean oil (Intralipid®) ². Some of the components of soybean oil are believed to be implicated in the pathogenesis of PNAC. Their high content of ω -6 polyunsaturated long chain fatty

acids may exert pro-inflammatory effects and plant sterols from soy may reduce bile flow and both factors were linked to the development of PNAC⁸.

5.1.5. Fish oil based intravenous lipid emulsions

In recent years, ILEs containing fish oil were proposed for treatment of PNAC in pediatric patients mainly suffering from short gut syndrome. Two research groups consecutively described the successful treatment of severe PNAC in neonates using Omegaven®^{9,10} an ILE composed exclusively of fish oil. The rationale behind the positive effects observed is built on their high content of ω -3 fatty acids which act anti-inflammatory and are thought to improve bile flow¹¹. However, whether fish oil or only replacement of soybean oil based ILE in PN⁶ caused the improvement in these patients, cannot be concluded. Prospective trials are required to substantiate the evidence⁸.

5.1.6. Preventing PNAC in ELBW infants

In view of their high risk to develop PNAC, ELBW infants could profit from a prophylactic intervention. Based on the promising results in the treatment of PNAC, ILEs based on fish oil seem attractive candidates. However, an ILE based on 100% fish oil like Omegaven® may deliver not enough ω -6 fatty acids and therefore cannot be used as the exclusive ILEs for nutrition of ELBW infants⁸.

With a broader panel of ILEs available today, a mixture of fishoil with soybean oil, medium chain triglycerides and olive oil (SMOFLipid®) has recently emerged. A prospective study in a total of 60 preterm infants showed that PN with SMOFLipid® induced lower serum γ -glutamyl transferase levels compared to controls receiving a soybean oil based ILE, suggesting a favourable influence on cholestasis and liver function¹². A prospective randomized trial in 28 pediatric patients demonstrated a reduction in total bilirubin levels using SMOFLipid® compared to a soybean oil based ILE¹³. Importantly SMOFLipid® is registered for PN of preterm infants, which makes a direct comparison of Intralipid® and SMOFLipid® in these vulnerable patients ethically acceptable¹⁴.

5.1.7. Fish oil and neurocognitive development

Long Chain polyunsaturated fatty acids (LC-PUFA) are both structural and functional lipids playing an important role in growth and development of the fetus and the newborn. In particular the 22:6 ω 3-LC-PUFA docosahexaenoic acid (DHA) is deemed to be crucial for a normal development of the fetal brain. *In utero*, high amounts of DHA cross the placenta in the last trimester. After birth mother's milk is the most important source¹⁵.

Preterm infants – as their endogenous capacity to synthesize DHA from precursor fatty acids is limited – depend on exogenous supply¹⁶. In this context, preterm infants accumulate a deficit of up

to 44% compared to *in utero* accretion rates¹⁶. In view of the documented correlation of DHA deficit and low birth weight¹⁶ ELBW infants are at particular risk, as they depend PN for several weeks and DHA is absent in the traditional soybean oil based ILEs. As the only source of DHA for the preterm infant is mother's milk or preterm formula and not ILEs, the prolonged time until full enteral feeds are established in these patients seems particularly critical.

Therefore an ILE like SMOFLipid® containing fish oil that provides DHA would reduce this deficit and may therefore confer potential benefits for the neurocognitive development.

5.1.8. Current Status of research on fish oil and parenteral nutrition associated cholestasis in preterm infants

There are currently no studies published on a fish oil containing ILE for prophylaxis of PNAC.

There is growing supportive evidence for treatment of established PNAC using ILE based on fish oil in pediatric patients from two observational and one prospective clinical trial, but there are no data from preterm infants.

The growing belief in a therapeutic effect of fish oil containing ILEs on PNAC is based on the published experience of clinicians from Boston around Mark Puder¹¹ and Toronto around Paul Wales⁹. They both described neonates with severe short gut syndrome and PNAC that dramatically improved after replacing some of the 100% soybean oil based ILE "Intralipid®" with a 100% fish-oil based ILE (Omegaven®) (Toronto) or completely switching over to a fish oil based ILE (Boston). The Boston group reported a resolution of cholestasis in 45-61 % (published cases: 60)^{10,17}. The Toronto group reported a rate of resolution of 63% (published cases: 22)¹⁸. Pooling these cases together, a mean of 53.6 % (44/82) of patients showed reversal of cholestasis. For comparison, historical cohorts of comparable patients who received the soybean oil based Intralipid® for PN, showed resolution of cholestasis only in 5-33 % during the disease course (published cases: 47)^{10,17}.

The only prospective trial using a mixed ILE containing fish oil (SMOFLipid®) in pediatric patients reported a significant reduction of total bilirubin levels compared with the soybean oil based ILE Intralipid®¹³.

The only prospective study performed in a population of preterm infants was performed by Tomsits et al¹². In healthy preterm infants (birth weights 1000 – 2500 gramm) they demonstrated good clinical tolerance and lower γ -glutamyl transferase levels using SMOFLipid® compared to standard care with Intralipid®. Though liver function was only a secondary outcome parameter of the study and the observational period was too short to assess any effect on PNAC, this finding supports a prophylactic effect of SMOFLipid® on liver function, underlining the need for further investigations.

5.1.9. Current Status of research on fish oil and neurodevelopment of preterm infants

There are currently no studies on long term neurodevelopment of preterm – in particular ELBW - infants after using a fish oil containing ILE.

There are prospective trials on enteral supplementation with LC-PUFA containing DHA from fish oil in preterm infants and during pregnancy with mixed results ^{15,19}.

Clinical studies in preterm infants focused on enteral supplementation of LC-PUFAs (including DHA) from fish oil in formula feedings. In this context, a Cochrane Review in 2008 by Simmer et. al ¹⁹ concluded that currently there is no convincing evidence of a sustained improvement of neurodevelopment by LC-PUFA supplementation. However, as the mean birth weight of preterm infants enrolled in these studies was consistently > 1000 gram (1074 – 1980) the authors stressed that ELBW infants should be investigated ¹⁹. In this context, there is indirect evidence from two prospective randomized trials, that supplementation of pregnant women with fish oil converts a beneficial effect on later neurodevelopment of their children ¹⁵. In line with the evidence from these trials, using an ILE containing fish oil for parenteral nutrition of ELBW infants could close the gap until ELBW infants are fully nourished with mother's milk or formula (supplemented with LC-PUFA). A reduction of the DHA deficit these infants normally accumulate ¹⁶ may confer a benefit to neurodevelopment.

5.2 Study rationale

Primary endpoint:

ELBW infants are at high risk for development of parenteral nutrition associated cholestasis (PNAC). There is growing evidence for a positive effect of fish oil based intravenous lipid emulsions (ILE) for the treatment of PNAC. Primary use of a fish oil containing ILE for PN may prevent the development of PNAC.

Secondary Endpoint:

ELBW infants accumulate a deficit of ω 3-LC-PUFA (especially DHA), which are important for neurodevelopment. An ILE containing fish oil provides these fatty acids and would reduce the deficit in ELBW infants, which may improve their neurocognitive development.

6. STUDY OBJECTIVES

6.1 Primary Objective

To investigate whether ELBW infants treated with two different ILEs (investigational drug: SMOFLipid®, comparative drug: Intralipid®) differ in the occurrence of PNAC (conjugated bilirubin > 1.5 mg/dl, measured on two consecutive occasions).

6.2 Secondary Objectives

To investigate whether ELBW infants treated with two different ILEs (investigational drug: SMOFLipid®, comparative drug: Intralipid®) differ in their neurodevelopment (Bailey Scales of Infant Development II) at 12 and 24 months of corrected gestational age

7. STUDY DESIGN

7.1 Study population

7.1.1 Subject population

Population: Extreme low birth weight (ELBW) infants

Recruitment: About 90 ELBW infants are admitted to our unit each year in the first 24 hours of life.

We expect to recruit 90 % (81 patients/a year) to the study.

Drop Outs: Based on a mortality of 22% in 2010 (Klebermasz K., unpublished data) and a conservative calculation, we expect 18/81 patients to drop out, leaving 63 patients a year for analysis of the primary outcome. We do not expect any other reasons for drop out.

Losses to follow up: 63 patients are expected to be discharged from hospital each year. Based on a follow up rate of 60% after discharge in 2009 (Fuiko R, unpublished data), we expect about 38/63 patients to be available for analysis of the secondary outcome each year. In the end we expect to lose 80/200 patients to follow up.

7.1.2 Inclusion criteria

- Infants with a birth weight ≤ 1000 Gram
- Admission to the neonatal ward in the first 24 hours of life
- Randomization on the respective study drug in the first 5 days of life

7.1.3 Exclusion criteria

Triplets or higher

Conjugated bilirubin > 1.5 mg/dl before inclusion to the study

Conditions associated with cholestasis independent of parenteral nutrition:

- Inborn errors of metabolism
- Viral Infections (cytomegaly virus, HIV, Hepatitis B, C)
- Immune mediated hemolytic disease (e.g. Rhesus incompatibility)
- Diagnosis of cystic fibrosis
- Primary cholestatic diseases of the liver

At follow up:

- Congenital neurological malformations will be excluded from follow up analysis (except screening for adverse events)

7.1.4 Study duration

The interventional phase starts with randomization on the study drug in the first 5 days of life and ends with discontinuation of PN, typically after 6 weeks (mean 44 days +/- SD 34 days, personal data).

The follow up phase ends at 24 months (2 years) of corrected gestational age.

7.1.5 Withdrawal and replacement of subjects

Criteria for withdrawal

Premature discontinuation from the study is to be understood when the subject did not undergo End of Study (EOS) examination and / or all pivotal assessments during the study.

Subjects must be withdrawn under the following circumstances:

- at their parent's request at any time
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the study personal
- if the subject is transferred to another hospital before parenteral nutrition is discontinued
- if the study drug was not provided < 80% of time as planned per protocol
- If an exclusion criterion is met, after inclusion to the study (except neurological malformation which only leads to withdrawal from follow up analysis except screening for adverse events)
- death before day of life 28

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records. Should the study be discontinued prematurely, all study materials (complete, partially completed and empty CRFs) will be retained.

Follow-up of patients withdrawn from the study

In case of premature discontinuation after study drug intake, the investigations scheduled for the EOS visit will be performed 7 +/-4 days after study drug discontinuation. The subjects will be advised that participation in these investigations is voluntary. Furthermore, they may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected in the course of the study will be destroyed.

Replacement policy

Patients withdrawn from the study < 28 days (outcome cannot be calculated) will be replaced and the next free subject number will be allocated. Drops outs will be included in the sample size. If patients are withdrawn from the study and the outcome can be calculated, (more than two blood samples taken), they will be considered in the intention to treat analysis (see chapter 10)

7.1.6 Premature termination of the study

The sponsor has the right to close this study at any time. The IEC and the competent regulatory authority must be informed within 15 days of early termination.

The trial or single dose steps will be terminated prematurely in the following cases:

- If adverse events occur which are so serious that the risk-benefit ratio is not acceptable.
- If the number of dropouts is so high that proper completion of the trial cannot realistically be expected.

8. METHODOLOGY

8.1 Study medication

Active agent and characteristics:

Investigational Product

Trade name of the agent:	SMOFLipid 200 mg/ml Emulsion zur Infusion
Manufacturer:	Fresenius Kabi Austria GmbH
Drug supply:	Fresenius Kabi Austria GmbH
Storage Instructions:	Do not freeze, do not store > 25° Celsius, protect from light
Route of administration:	Intravenous

Comparator

Trade name of the agent:	Intralipid 20% - Emulsion zur Infusion
Manufacturer:	Fresenius Kabi Austria GmbH
Drug supply:	Fresenius Kabi Austria GmbH
Storage Instructions:	Do not freeze, do not store > 25° Celsius, protect from light
Route of administration:	Intravenous

8.1.1 Dosage and administration

Initial dose:	1 g/kg/d (= 5 ml/kg/d)
Maintenance dose:	3 g/kg/d (=15 ml/kg/d)
Route of administration:	Intravenous
Duration:	As long as parenteral nutrition is needed

8.1.2 Study-drug up- and down titration

According to a stepwise increase or reduction of enteral feedings a proportional increase or reduction of parenteral nutrition will be performed including a reduction of the study drug / comparator. The study drug/comparator will be finished as soon as full enteral feeds are reached and PN is stopped (at 140-160 ml/kg/d of total fluid volume depending on the fluid needs of the infant).

8.1.3 Study drug interruption or discontinuation

The investigator must temporarily interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient. The interruption or premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., laboratory abnormalities), or for administrative reasons, in particular withdrawal of the patient's consent.

Hypertriglyceridemia: The study drug will be interrupted for 24 hours at triglyceride levels > 400 mg/dl or down titrated at triglyceride levels of 251-400 mg/dl. Control measurements of triglyceride levels will be performed in the next 24-72 hours to control for successful normalization of triglyceride levels under parenteral nutrition.

The reason for study drug interruption or premature permanent discontinuation must be documented in the CRF.

8.1.4 Study drug premature permanent discontinuation

Study drug premature permanent discontinuation due to an adverse event

If the reason for premature permanent discontinuation of study treatment is an AE, the patient should have a "Premature End of Study (EOS)" visit with all the assessments performed before the study drug discontinuation, whenever possible.

Study drug premature permanent discontinuation due to another reason than adverse event

If the reason for premature permanent discontinuation of study treatment is not an AE, the patient should be withdrawn from the study (withdrawal of consent) and have the end of study (EOS) visit with all the assessments performed before the study drug discontinuation, whenever possible.

8.1.5 Study-drug delivery & drug storage conditions

The study drug will be delivered from the supplying company to the investigators and stored at room temperature under controlled conditions (22°C +/- 3°C) in a locked room. A min/max thermometer will be used to control for temperature in the storage room. Full documentation of delivery, storage and disposition will be maintained.

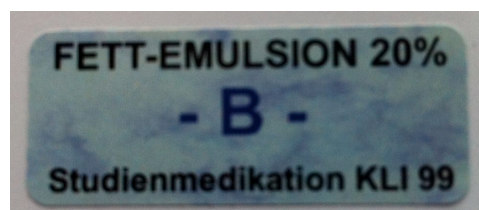
8.1.6 Study drug packaging and labeling

The study drugs are delivered in sterile glass containers of 100 ml by the manufacturer and will be re-labelled at the study site as described in section 8.3. Storage is described in section 8.1.5. For application to study subjects, the study drugs will be brought to the neonatal wards by a member of the blinding team. For IV application, the study drugs will be transferred from the re-labelled commercial containers to perfusor syringes connected to perfusor lines suitable for IV application. Perfusor syringes will be labelled (see sample labels 1 and 2 below). Preparation for IV application will be done in a laminar air hood under sterile conditions by trained intensive care nurses, forming part of the blinding team.

Sample Label Number 1



Sample Label Number 2



8.1.7 IMP administration & handling

The IMP or comparator must not be frozen or stored > 25° C, application is performed in light protected perfusor syringes and perfusor lines. Application may be performed IV via central and peripheral venous catheters. The IMP or comparator must not be mixed with any other drug besides the commercially available vitamin solutions "Soluvit N" and "Vitalipid" (Fresenius Kabi Austria GmbH).

8.1.8 Drug Accountability

Drug Accountability will be recorded at on-going basis on paper form/source data, Drug dispensing have to be entered into the CRF. Furthermore the correct intake of IMP or any variations concerning that will be recorded in the CRF at each visit during treatment period

8.1.9 Procedures to assess subjects compliance

Whether the IMP or comparator were administered correctly will be followed from the documentation in the electronic patient documentary system used at the neonatal ICU.

8.1.10 Concomitant medication

The well-being of the patient has the first priority, and modifications of concomitant treatment during the trial are allowed as necessary. They should be documented in the patient's records.

In case of cholestasis (i.e. conjugated bilirubin two times > 1.5 mg/dl),

Ursodeoxycolic acid at 20-30 mg/kg/day is the treatment of choice.

Omegaven® is allowed as add on at 1g/kg/d, if conj. bilirubin > 6 mg/dl,

8.2 Randomization and stratification

On day 0, patients are randomized to one of the two study groups and the study medication is provided. Study subjects will be block randomized (ratio 1:1) and stratified according to sex and birth weight (in two groups: < 750 gram vs. ≥ 750 gram) using an online randomization programme provided by the Center for Medical Statistics, Informatics, and Intelligent Systems of the Medical University of Vienna. In case of twins, randomization will be applied to the firstborn; the twin will be assigned to the other treatment group.

8.3 Blinding

Blinding of subjects, investigators and outcome assessors will be performed as follows:

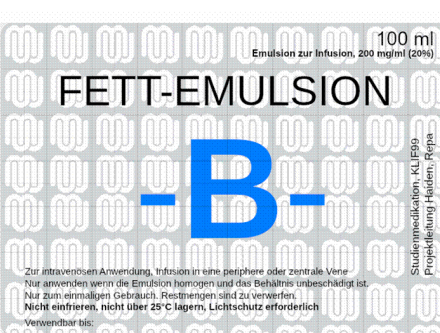
First re-labelling of the study drug containers (see sample label 1 and 2 below) will be performed by two members of the blinding team not involved in the collection of data, treatment of study subjects or preparation of the study drugs for IV application. The study drugs are kept in glass containers of 100 ml and will be re-labelled with samples as indicated (see sample label 1 and 2 below) and stored as described (section 8.1.5).

Second, for delivery to study subjects the study drugs will be brought to the wards by a member of the blinding team, where the preparation for IV application will be done in a laminar air hood by a member of the blinding team as described in section 8.1.7. As intensive care nurses involved in caretaking of the patients form part of the blinding team, nursing caregivers are not blinded. Medical doctors prescribing the daily amounts of the IMP remain blinded.

Sample Label Number 1



Sample Label Number 2:



8.3.1 Emergency procedure for unblinding

If unblinding of a study participant is required due to an emergency, the code can be broken by the Investigator. Code breaking will be fully documented.

8.3.2 Unblinding at the end of the study.

Codes will be broken after data analysis of the primary outcome, this is after the last patient has finished active phase. Investigators involved in assessment of data in the follow up phase (secondary outcome neurodevelopment) will remain blinded.
~~Codes will be broken after the close-out Monitoring Visit and the cleaning of the database.~~

8.4 Benefit and risk assessment

8.4.1 Benefit for the patient

If the hypothesis is correct, participating patients receiving the study medication will benefit from a reduced risk of developing liver injury due to long term parenteral nutrition. They will benefit from a improved long term neurodevelopment.

8.4.2 Risk for the patient

The drug under investigation fulfilled the criteria for registration for application in preterm infants. Therefore, risk for patients receiving the study drug should not be higher compared to standard care. In the worst case we expect that there will be no benefit.

8.5 Study procedures

8.5.1 General rules for trial procedures

- All study measures like blood sampling and measurements (ultrasound etc.) have to be documented with date (dd:mmm:yyyy).
- In case several study procedures are scheduled at the same time point, there is no specific sequence that should be followed.
- The dates of all procedures should be according to the protocol. The time margins mentioned in the study flow chart are admissible. If for any reason, a study procedure is not performed within scheduled margins a protocol deviation should be noted, and the procedure should be performed as soon as possible or as adequate.
- If it is necessary for organizational reasons, it is admissible to perform procedures which are scheduled for one visit at two different time points. Allowed time margins should thereby not be exceeded.

8.5.2 Screening investigation

At screening, the patient's demographic data and lab results (see Section 7.1.2 and 7.1.3 Inclusion and Exclusion Criteria) will be evaluated for eligibility to the study.

8.5.3 End-of-study (EOS) examination

At discharge of the patient from hospital, patients undergo the end-of-study examination that entails Weight, crown heel length, head circumference and a basic blood test (red and white blood count, liver function tests, electrolytes) performed in clinical routine in all ELBW infants.

8.5.4 Laboratory Tests

Blood counts and complete blood chemistry is routinely performed according to the local standard of care at the unit at least every 10 +/-4 days until discharge from hospital. No additional blood sampling or analyses will be performed in study subjects in comparison to standard of care of ELBW infants.

All laboratory parameters of interest for the study routinely performed are:

denomination	Variable	time of measurement
Conjugated bilirubin	mg/dL	every 7-14d until discharge
ALAT	U/L	every 7-14d until discharge
ASAT	U/L	every 7-14d until discharge
γ-glutamyltransferase	U/L	every 7-14d until discharge
Alkaline phosphatase	U/L	every 7-14d until discharge
Triglycerides	mg/dL	every 7-14d until discharge

Additional parameters used for the study

All additional parameters of interest are documented or produced routinely during the patient's admission to the unit or follow-up according to the local standard of care. No additional interventions will need to be performed.

denomination	Variable	time of measurement
<u>Basic demographic data</u>		
Sex	m/f	at birth
Gestational age	days	at birth
Twin	yes/no	at birth
Mode of delivery	caesarean/spontaneous	at birth

Prenatal steroids for lung maturation	yes/no	at birth
Birth weight	gram, Z Score	at birth
Birth crown heel length	cm, Z Score	at birth
Birth head circumference	cm, Z Score	at birth
Small for gestational age	yes/no	at birth
Apgar scores at 1, 5 and 10 minutes	0-10	at birth
Umbilical artery pH at birth	range 6.7 – 7.6	at birth

Growth and nutrition parameters

Time on parenteral nutrition	days	at discharge
Total amount of parenteral lipids	gram	at discharge
Enteral nutrition in 1 st first week of life	ml/day	day 0-6
Weight at discharge	gram, Z Score	at discharge from hospital
Crown heel length at discharge	gram, Z Score	at discharge from hospital
Head circumference at discharge	gram, Z Score	at discharge from hospital

Death > 28 days	yes/no	day of life 28 - discharge
(Death before 28 days = drop out)		
If death	day of life	day of life 28 - discharge

Neonatal (preterm) morbidities

Intraventricular hemorrhage Grad 3/4	yes/no	at discharge
Cystic periventricular leucomalacia	yes/no	at discharge
Chronic lung disease	yes/no	at discharge
Received steroids for chronic lung disease	yes/no	at discharge
Treatment for pulmonary hypertension (Sildenafil, iNO)	yes/no	at discharge
Culture proven sepsis	yes/no	at discharge
Necrotizing enterocolitis Bell's Stage ≥ IIa	yes/no	at discharge
Focal intestinal perforation	yes/no	at discharge
Abdominal surgery	yes/no	at discharge
Ibuprofen for PDA	yes/no	at discharge
Surgical ligation of PDA	yes/no	at discharge
Highest ROP Grade	0-5	at discharge
ROP treated with laser	yes/no	at discharge

<i>Gastrointestinal disorders</i>		Lack of appetite, nausea, vomiting		
<i>Vascular disorders</i>			Hypotension, hypertension	
<i>General disorders and administration site conditions</i>	Slight increase in body temperature	Chills	Hypersensitivity-reactions (e.g. anaphylactic or anaphylactoid reactions, skin rash, urticaria, flush, headache), heat or cold sensation, paleness, cyanosis, pain in the neck, back, bones, chest and loins	
<i>Reproductive system disorders</i>				Priapism

9.1.2 Definition of adverse events

An AE is any untoward adverse change from the subject's baseline condition, i.e., any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Pre-planned interventions or occurrence of endpoints specified in the study protocol are not considered AE's, if not defined otherwise (eg. as a result of overdose)
- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

9.2 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines and WHO GCP guidelines as any AE fulfilling at least one of the following criteria:

- Results in deaths.
- Life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring subject's hospitalization or prolongation of existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Resulting in persistent or significant disability or incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Is medically significant or requires intervention to prevent at least one of the outcomes listed above.

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

9.2.1 Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.

An additional overnight stay defines a prolongation of existing hospitalization.

Hospitalization as criterium for SAE classification severely limited in this study. In this study, patients are hospitalized from study start until end of treatment. Hospitalization – prolongation of existing hospitalization should be applied as criterium for SAE classification only in case of AEs directly leading to a prolongation of hospitalization.

The criterium should not be applied to AEs occurring during the routine hospitalization.

The following is not considered an SAE and should be reported as an AE only:

- Treatment on an emergency or outsubject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

9.2.2 SAEs related to study-mandated procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are all serious adverse reactions with suspect causal relationship to the study drug that is unexpected (not previously described in the SmPC - Summary of Product Characteristics or Investigator's brochure) and serious.

9.3 Severity of adverse events

The severity of clinical AEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled in with the intensity observed during study drug administration.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE resolves spontaneously or may require minimal therapeutic intervention;

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

9.4 Relationship to study drug

For all AEs, the investigator will assess the causal relationship between the study drug and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow known response pattern to the suspect study drug (if response pattern is previously known).
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Unlikely
- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically not very plausible
- May be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Possible related

- Follows a reasonable temporal sequence form administration of the study drug.
- May follow a known response pattern to the study drug (if response pattern is previously known).
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable.
- Probable
- Follows a reasonable temporal sequence form administration of the study drug.
- Follows a known response pattern to the study drug (if response pattern is previously known).
- other causes for the event are unlikely

Definitely related

- Follows a reasonable temporal sequence form administration of the study drug.

- Follows a known response pattern to the study drug (if response pattern is previously known).
- No other reasonable cause is present.

9.5 Reporting procedures

A special section is designated to adverse events in the case report form. The following details must thereby be entered:

- Type of adverse event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- Relation to study drug (unrelated, possibly related, definitely related)

Adverse events are to be documented in the case report form in accordance with the above mentioned criteria.

9.5.1 Reporting procedures for SAEs

In the event of serious, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the clinical investigator immediately. The following details should at least be available:

- Patient initials and number
- Patient: date of birth, sex, ethical origin
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious
- Short description of the event and outcome

If applicable, the initial report should be followed by the Follow up report, indicating the outcome of the SAE.

9.5.2 Reporting procedures for SUSARs

It must be remembered that the regulatory authorities, and in case of SUSARs which could possibly concern the safety of the study participants, also the Institutional Review Board / Independent Ethics Committee (IRB / IEC) are to be informed. Such reports shall be made by the study management and the following details should be at least available:

- Patient initials and number
- Patient: date of birth, sex, ethical origin
- Name of investigator and investigating site
- Period of administration

- The suspected investigational medical product (IMP)
- The adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship to the IMP
- Concomitant disease and medication
- Short description of the event:
 - Description
 - Onset and if applicable, end
 - Therapeutic intervention
 - Causal relationship
 - Hospitalization or prolongation of hospitalization
 - Death, life-threatening, persistent or significant disability or incapacity

Electronic reporting should be the expected method for reporting of SUSARs to the competent authority. In that case, the format and content as defined by Guidance (28) should be adhered to. The latest version of MedDRA should be applied. Lower level terms (LLT) should be used.

9.5.3 Annual Safety Report

The Annual Safety Report will be provided by the principal investigator at least once a year. This report will also be presented annually to the Independent Ethics (IEC) and to the competent authorities by the sponsor.

10.FOLLOW-UP

10.1 Follow-up of study participants including follow-up of adverse vents

All study participants will be followed up to 24 months of corrected gestational age to assess neurodevelopment, growth parameters and ophthalmologic exams (visual development (according to the standards of our follow – up outpatient clinic for extremely premature infants. SAEs including death will be monitored. Adverse events will be followed until they have been completely resolved or stabilized according to the investigators discretion.

10.2 Treatment after end of study

There is no treatment after the end of the study

11.STATISTICAL METHODOLOGY AND ANALYSIS

11.1 Analysis sets

Two different analysis sets are defined:

(Modified) Intention to treat set

This analysis set includes all subjects where the outcome can be calculated (more than two blood samples taken), even though the subject was not observed the full 18 weeks.

Per-protocol set

This analysis set comprises all subjects who were observed the full 18 weeks, received the study drug as planned and did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary objective, i.e., without major protocol violations.

11.2 Sample size considerations

Data investigating the incidence of PNAC in our unit showed an incidence of 25 % from 2007-9 (unpublished data). We considered a difference of 15% between the groups (incidence of PNAC: 25% for Intralipid and 10% for SMOFLipid, respectively) as a clinically relevant effect. A sample size estimation based on a χ^2 -test indicated that 200 infants (100/group) are required to detect a difference of 15% between the groups with a power of 80% and a significance level of 0.05. The estimated drop out rate is 22%. Therefore, a sample size of 122 patients per group is planned. For sample size estimation, data were assumed to be independent.

11.3 Relevant protocol deviations

Protocol deviations will have to be documented and should be discussed with the Sponsor.

All protocol deviations will be listed in the study report and reported to the sponsor.

11.4 Statistical analysis plan

A **statistical analysis plan (SAP)** will provide full details of the analyses, the data displays and the algorithms to be used for data derivations. The SAP furthermore will include definitions of major and minor protocol deviations and the link of deviations to the analysis set, which also will be covered in the final study report.

Procedures of reporting any deviations from the original statistical plan (any deviations from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate.

The SAP should preferably be a separate document. In the protocol this document should be referenced. Alternatively the SAP could be fully included in the study protocol.

11.5 Missing, unused and spurious data

If less than two blood samples of a patient were taken, the outcome cannot be calculated and therefore, this patient will be excluded from the analysis. The analysis will be carried out per protocol.

If the outcome of a patient can be calculated (more than two blood samples taken) but the patient was withdrawn from the study before week 18, analysis will be carried out 1) by intention to treat analysis, with the duration of treatment as additional covariable and 2) per protocol.

11.6 Endpoints analysis

11.6.1 Primary endpoint analysis

A χ^2 -test will be used for analysis of the primary outcome PNAC.

Additionally, the effect of treatment and other relevant influence factors (i. e. duration of parenteral nutrition, birth weight, amount of enteral feeds in the first week of life) on the primary endpoint will be analyzed using a logistic regression model with stepwise selection

In case of twins, the analysis will be carried out 1) as mentioned above, but only including the firstborn and 2) by calculating a generalized linear model with mother as random factor.

11.6.2 Secondary endpoint analysis

Bailey Scales of Infant Development II at 12 and 24 months: Differences in the scores of psychomotor development and neurocognitive development, respectively, between the groups will be analyzed by repeated measures ANOVA, also accounting for confounders (e.g. birth weight, IVH Grade 3/4, cystic periventricular leucomalacia, NEC). In case of twins, the analysis will be carried out 1) as mention above, but only including the firstborn and 2) by calculating a mixed model with mother and child as random factor. In case of too many drop outs, descriptive statistics will be carried out.

For Gross Motor function measurements at 12 and 24 months, descriptive statistics will be conducted.

11.6.3 Safety and tolerability endpoints

Hypertriglyceridemia: Peak level in mg/dl

11.6.4 Baseline parameters and concomitant medications

The following parameters will be investigated:

Sex (m/f)

Age at birth (gestational weeks + days)

Twin (yes/no)

Mode of delivery (caesarean section/spontaneous delivery)

Received any prenatal steroids for lung maturation (yes/no).

Weight (gram) at birth

Length (cm) at birth

Head circumference (cm) at birth

Small for gestational age (< 10. percentile birth weight, yes/no)

Apgar scores at 1, 5 and 10 minutes (0-10)

Umbilical artery pH

Concomitant medications and changes in concomitant medication will be documented by the Investigator.

11.7 Interim analysis

No interim analysis planned.

11.8 Software program(s)

SAS 9.2

Microsoft Excel

12.DOCUMENTATION AND DATA MANAGEMENT

12.1 Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

12.1.1 Case report form (CRF)

For each subject enrolled, regardless of study drug initiation, a paper CRF must be completed and signed by the investigator or a designated sub-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis.

CRF entries and corrections will only be performed by study site staff, authorized by the investigator. In a "Paper-CRF" all forms should be completed and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator, co-investigator or study nurse.

The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately.

The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site.

Completed CRFs will be passed to the Statistician for further analysis.

12.1.2 Data Collection

Data collected at all visits are entered into an interactive form. The CRFs will be source documents verified following guidelines established before study onset as detailed in the Monitoring Plan.

12.2 Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified (according to ICH-GCP “essential documents”). These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the protocol/amendments, EudraCT forms, CRFs (eCRF printout), standard operation procedures (SOPs), data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH/Good Clinical Practice (GCP) and local regulations.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (in Austria 15 years after discontinuing clinical development or after the last marketing approval). If source documents are not durable as long as needed (e.g. ECG printouts) they must be preserved as a copy. No study document should be destroyed without prior written approval from the Department of

When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

12.3 Quality Control and Quality Assurance

12.3.1 Periodic Monitoring

According to GCP at least 3 monitoring visits are scheduled. An initiation visit, one routine visit and a close out visit after the last patient has finished the study or data base lock.

The designated monitor will contact and visit the investigator regularly and will be allowed to have access to all source documents needed to verify the entries in the CRFs and other protocol-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals according to the monitoring plan throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main efficacy, safety, and tolerability endpoints. The monitor will be working according to SOPs and will provide a monitoring report after each visit for the Sponsor. Depending on the quality of the data, additional monitoring visits may be necessary according to the sponsor's discretion. The investigator will resolve discrepancies of data.

Monitoring will be performed by Koordinierungszentrum für Klinische Studien on a regular basis and will follow a detailed Monitoring Plan.

12.3.2 Audit and Inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

12.4 Reporting and Publication

12.4.1 Publication of study results

The findings of this study will be published by the sponsor (investigators) in a scientific journal and presented at scientific meetings. The manuscript will be circulated to all co-investigators before submission. Confidentiality of subjects in reports/publications will be guaranteed.

13. ETHICAL AND LEGAL ASPECTS

13.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical trial, a patient's caregiver (mother or father) must give written consent to participation in the study.

During the instruction the trial participants are to be made aware of the fact that they can withdraw their consent – without giving reasons – at any time without their further medical care being influenced in any way.

In addition to the comprehensive instructions given to the trial participants by the investigator, the trial participants also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.

The patients must agree to the possibility of study-related data being passed on to relevant authorities.

The patients must be informed in detail of their obligations in relation to the trial participants insurance in order not to jeopardize insurance cover.

13.2 Acknowledgement / approval of the study

The investigator (or a designated CRO) will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee

(EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study.

The clinical trial shall be performed in full compliance with the legal regulations according to the Drug Law (AMG - Arzneimittelgesetz) of the Republic of Austria.

An application must also be submitted to the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG) represented by the Agency for Health and Food Safety (AGES PharmMed) and registered to the European Clinical Trial Database (EudraCT) using the required forms. The timelines for (silent) approval set by national law must be followed before starting the study.

13.2.1 Changes in the Conduct of the Study

Protocol amendments

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Study Termination

If the sponsor or the investigator decides to terminate the study before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or (designated CRO on behalf of the sponsor) will notify the relevant CA and EC. Documentation will be filed in the Trial Master and Investigator Files.

Clinical Study Report (CSR)

Within one year after the final completion of the study, a full CSR will be prepared by the sponsor and submitted to the EC and the competent authority.

The Investigator will be asked to review and sign the final study report.

13.3 Insurance

During their participation in the clinical trial the patients will be insured as defined by legal requirements. The investigator of the clinical trial will receive a copy of the insurance conditions of the 'patients insurance'. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

Details on the existing patients insurance are given in the patient information sheet.

Patients will be insured by the Zürich-Versicherung (Nr. 07229622-2) according to the Austrian law. Please indicate insurance details!

13.4 Confidentiality

The information contained in this document, especially unpublished data, is the property of the sponsor. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

13.5 Ethics and Good Clinical Practice (GCP)

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008) and with the laws and regulations of the country in which the clinical research is conducted.

The investigator of the clinical trial shall guarantee that only appropriately trained personnel will be involved in the study. All studies must follow the ICH GCP Guidelines (June 1996) and, if applicable, the Code of Federal Regulations (USA). In other countries in which GCP Guidelines exist, the investigators will strictly ensure adherence to the stated provisions.

Therefore this study follows the EU Directive embedded in the Austrian drug act.

14.APPENDICES

Appendix 1. Informed Consent Form (Version 1.0; Date 8.11.11)

Appendix 2. Summary of product characteristics

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