Title Page

Protocol Title:

THeophyllIne Effects in the Fontan circulation

A single group treatment phase 2 single-arm no-masking study to assess safety and efficacy of a short-term oral treatment with theophylline (ATC-no. R03D A04) in terms of improvements in cardiorespiratory fitness, health-related quality of life, cardiac performance and respiratory function in male and female adolescents aged 16 to 25 years with a Fontan-type surgical palliation of univentricular congenital heart disease.

Protocol Number: 5.1 (May 5, 2023)

Amendment Number: 02

Compound: Theophylline (ATC R03D A04)

Brief Title:

THeophyll**I**ne **EF**fects in the Fontan circulation - potential improvements in cardiorespiratory fitness, health-related quality of life, cardiac performance and respiratory function from oral treatment with theophylline in adolescent males and females with Fontan-type palliation of univentricular congenital heart disease

Study Phase: phase 2 / pilot

Acronym: **THIEF pilot study**

Sponsor Name: Oslo University Hospital

Legal Registered Address: Postboks 4950 Nydalen, 0424 Oslo, Norway

Regulatory Agency Identifier Number(s)

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Sponsor Signatory:

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*29-08-2022*
Amendment 01, protocol version 4	*04-11-2022*
Amendment 02, protocol version 5	*28-03-2023*
Amendment 02, protocol version 5.1 in response to evaluation of substantial modifications from 28-03-2023	*05-05-2023*

Amendment 01 (substantial modification: (Nov 04, 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

A decision in the study team was made to use an electronic log book solution for better monitoring of participant compliance and AE's. This decision was made after initial trial application authorization.

Section # and Name	Description of Change	Brief Rationale
Signature page	Filled in correct contact details	Preliminary placeholders from protocol version 1 are replaced
Protocol Amendment Summary of Changes Table	A table and overview of amendment history has been added	Necessary change together with amendment no.1
1.1 Synopsis, Brief summary	Added information about electronic participant log book in ViedocMe (part of the eCRF database)	A decision in the study team was made to use an electronic log book solution. This decision was made after trial authorization.
4.1 Overall design	Added information about electronic participant log book in ViedocMe (part of the eCRF database)	A decision in the study team was made to use an electronic log book solution. This decision was made after trial authorization.
Whole document	Typographic and semantic errors and flaws including institutional name changes were corrected	(Non-substantial changes)

Amendment 02 (substantial modification: March 28, 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Initial screening visits of potential participants revealed frequent screening failure (6 out of 10 visits) due to biochemical exclusion criteria, namely elevated ammonia and/or mildly elevated INR in the absence of signs of moderate/severe liver disease by other biochemical (bilirubin, ALT) or imaging findings (MRI or ultrasound). The intention behind liver-related exclusion criteria was to exclude participants with either potential hepato-cellular carcinoma or with severe Fontan-associated liver disease with significantly impaired synthesis or significantly increased theophylline toxicity.

Experiences with repeated screening failure, experiences with the initial three enrolled participants, and a focused review of available scientific literature resulted in the following considerations:

- Porto-systemic shunting of enteral venous blood to the systemic venous system leads to elevated ammonia and should probably be expected frequently late (> 10 years) after the Fontan operation (Takefuta 2021) (1). Hence ammonia is not suited to discriminate different degrees of hepatic involvement in Fontan patients.
- In a previous study of hepatic and cardiac function in Fontan patients, spontaneous INR had a median of 1.2 equivalent to the upper normal range (Camposilvan 2008) (2). A spontaneous INR above the upper normal limit (>1.2) is probably a too restrictive exclusion criteria in a Fontan population. In addition, the use of direct oral anti-coagulant drugs may cause slightly elevated INR in the absence of warfarin treatment (Ofek 2017) (3).
- Bilirubin has been shown to correlate with slow theophylline clearance in cirrhotic patients (Mangione 1978) (4). Even in the absence of elevated ammonia and severe liver disease, a theophylline concentration within therapeutic range was achieved by 2/3 participants on a low starting dose (200 mg BID) or even after dose reduction from initial dosage (100mg BID)

Other practical protocol, recruitment and consent issues that became obvious during the first screening visits and inclusions (see table).

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis) 4.1 (Overall design) 6.5 (Dose modification)	Reduced starting dose of study drug depending on bilirubin level, and option to further reduce to OD depending on study drug concentration	Theophylline clearance has been demonstrated to correlate with bilirubin level, and 2/3 participants have achieved therapeutic theophylline concentrations on study drug dosage below recommended staring dose in adults

1.1 (Synopsis)	Removed mandatory gender ratio of 1:1	Both genders should be represented in study group, but no rationale for 1:1 existed
1.3 (Schedule of Activities)	Screening laboratory tests (more comprehensive compared to baseline and follow-up) might be collected locally and shipped to the study centre up to 28 days before screening visit and repeated on the day of visit if informed consent has been signed previously.	Our study design has been shown to allow for safe participant monitoring independently of travel distance to the study center. To avoid futile long-distance travel due to screening failure by laboratory results.
1.2 (Schedule of Activities) 4.1 (Overall design)	Home-based ECG-monitoring device is started during baseline visit	Recording of baseline ECG-readings with the monitoring device for comparison during treatment monitoring
1.3 (Schedule of Activities)	A time interval of 1-3 days for completing baseline visit with polygraphy has been defined with subsequent start of study medication	Practical / logistical difficulties to always perform polygraphy during first night after baseline visit (device shipping and device turnover between participants)
5.1 (Inclusion criteria)	Rephrasing of general liver-related criteria	Defining of only severe Fontan-associated liver disease as safety issue during theophylline use (corresponding to bilirubin-dependent study drug start dose)
5.2 (Exclusion criteria)	The upper limit of acceptable INR has been altered.	Some elevation of INR in the absence of severe liver disease has been described in Fontan patients and in patients using direct oral anticoagulative drugs
5.2 (Exclusion criteria)	Liver imaging exclusion criteria has been rephrased as “Hepato-cellular-carcinoma (HCC)-suspect lesions” by liver imaging.	The imaging-related exclusion criteria of “nodules > 10 mm” by MRI or ultrasound images have been difficult to apply to imaging reports from individual patient files. We noted frequent descriptions of lesions below/above 10 mm with altered perfusion, but without a nodular/expansive structure.

5.2 (Exclusion criteria)	Ammonia has been removed from biochemical exclusion criteria	Disease-specific alterations in liver circulation in patients with Fontan circulation have led to screening failure in an unexpected high percentage of potential participants due to elevated ammonia levels in the absence of severe liver disease.
5.5 (Screening failures)	Re-screening permitted	A rescreening option with optimized blood work circumstances will improve recruitment of participants with otherwise no signs of severe liver disease.
10.4.2 (Contraception Guidance)	Absence of opposite gender sexual activity during study period has been explicitly defined as sufficient contraception.	Unnecessary use of oral contraception in female Fontan patients must be avoided due to risk of thromboembolism.

Amendment 02 (May 5 2023, changes after evaluation of substantial modification from March 28, 2023)

Section # and Name	**Description of Change**	**Brief Rationale**
10.1.3. Informed Consent Process	The inclusion details of participants who reside at long distance from the study centre (but within 1 hour travel distance from nearest hospital) is described.	Unplanned study visits for those participants will require preparedness of local hospitals and health care providers of relevant specialty.
5.4. Screen Failures	The maximum number of rescreening attempts has been defined as being two.	To limit rescreening attempts.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

THeophyllIne Effects in the Fontan circulation (THIEF pilot study)

A single group treatment phase 2 single-arm no-masking study to assess safety and efficacy of a short-term oral treatment with theophylline (ATC-no. R03D A04) in terms of improvements in cardiorespiratory fitness, health-related quality of life, cardiac performance and respiratory function in male and female adolescents aged 16 to 25 years with a Fontan-type surgical palliation of univentricular congenital heart disease.

Brief Title:

THeophyll**I**ne **EF**fects in the Fontan circulation - potential improvements in cardiorespiratory fitness, quality of life, cardiac performance and respiratory function from oral treatment with theophylline in adolescent males and females with Fontan-type palliation of univentricular congenital heart disease

Rationale:

The effects of theophylline match in a remarkable way several pathophysiological mechanisms of Fontan failure. Hence, theophylline, even if it is an old and well-proven drug, is an intriguing substance to study for its potential to improve performance of the Fontan circulation, and it has not been studied in this context before.

Objectives, endpoints and Estimands:

Objectives	Estimands and Endpoints
Primary	
• To investigate feasibility and safety of a 12 weeks treatment study design with remote dosage titration and ambulatory heart rhythm monitoring during treatment phase	Endpoints: • Frequency of treatment emerged AE/SAE • Freedom from participant dropout based on tolerability of the study intervention • Number of participants requiring dose reduction after first serum concentration assessment • Freedom of arrhythmogenic side effects of the study treatment leading to patient dropout

Primary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on exercise capacity in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation.	Estimand: • Circulatory reserve during exercise Endpoint: • Difference in oxygen uptake at anaerobic/ventilatory threshold pre/post treatment.
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on quality of life in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation.	Estimand: • Health-related quality of life Endpoint: • Difference inn total scores from SF-36 and EQ-5D questionnaires
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on cardiac performance in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	Estimand • Cardiac performance at rest Endpoint • Ventricular function as assessed by echocardiography at rest
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on respiratory function including diffusion capacity in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	Estimand: • Pulmonary function Endpoint: • Diffusion capacity
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on sleep disordered breathing in adolescents aged 16-25 years with univentricular congenital	Estimand • Sleep apnea Endpoint

heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	• Change in Apnea Hypopnea Index during home-based sleep study pre-/post-treatment

Overall Design:

Single-group uncontrolled single-center open-label treatment study in adolescents (age 16-25 years) with univentricular congenital heart defects surgically palliated with a Fontan-type operation. Inclusion of eligible patients from inpatient and outpatient contacts at participating departments at Oslo University Hospital Rikshospitalet.
Study inclusion visit, drug treatment, remote dose adjustment, heart rhythm monitoring, and final post-treatment assessment study visit will be performed at the clinical research ward for children, Division of Paediatric and Adolescent Medicine. Data Monitoring by Clinical Trials Unit at Oslo University Hospital Research Support.
Dose adjustment decisions and heart rhythm monitoring will be effectuated by a joint group of associated specialists (pediatric cardiology, cardiology) with continuous service through the entire study period.

Brief Summary:

The purpose of this study is to assess safety and efficacy of a short-term oral treatment with theophylline for improvement of cardiorespiratory fitness, health-related quality of life, cardiac and respiratory function in adolescents with Fontan-type palliation of univentricular congenital heart disease.
The study hypothesis is that a 12-week oral treatment with theophylline improves the circulatory reserve in the Fontan which results in measurable improvement of cardiorespiratory fitness, health-related quality of life, cardiac and respiratory function.

Study details:

Study duration: approximately 18 months (depending on inclusion progress, from inclusion of first participant until final visit of last enrolled participant)

Individual treatment duration: 12 weeks

Visit frequency: two study visits, at inclusion and at end of treatment period

Number of Participants: Ten participants of both sexes will be enrolled and invited to the study inclusion visit to achieve an intervention group of 10 individuals starting the oral treatment. In terms of being a pilot study, the study will also help to estimate the expected fractions of evaluable and non-evaluable participant in a subsequent full scale randomized clinical trial. Evaluability means the participant absolving all included study tests during inclusion and final study visit and completing scheduled dosage control and ECG monitoring tasks.

Note: “Enrolled” means a participant’s or his/her legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Health measurement / observation:

At inclusion and final visit:

- Demographics, biometric data, medical history
- Quality of life assessment by questionnaire (SF-36, EQ-5D)
- Echocardiography for cardiac function assessment
- Pulmonary function test incl. diffusion capacity
- Cardiopulmonary exercise test (bicycle ergometer)
- Home-based polysomnography

During treatment phase:

- Dosage monitoring by analysis of theophylline concentration in blood sample (obtained locally) in addition to analysis of liver and renal parameters (ALT, bilirubin, creatinine), repeated on indication (after dose adjustment, in case of arrhythmic events)
- Treatment compliance and AE monitoring by symptom report in electronic participant log book in ViedocMe (part of the eCRF-database)
- ECG-monitoring (rhythm storage at least every hour) by tape-on ECG-device (ECG247®) connected to via smartphone app to an online database with 24/7 accessibility for medical monitor (5).
    - During early intervention phase until 5-7 days after therapeutic through concentration is achieved, the participant will continuously use the ECG247 device. In case of symptoms (palpitations or other arrhythmia-suspect symptoms), the participant will be able to notify the medical monitor (cardiologist) for immediate review of ECG readings.
    - After cessation of continuous ECG-monitoring, the participant will be equipped with additional ECG-tapes for symptom-initiated ECG-readings and contact with medical monitor as needed.

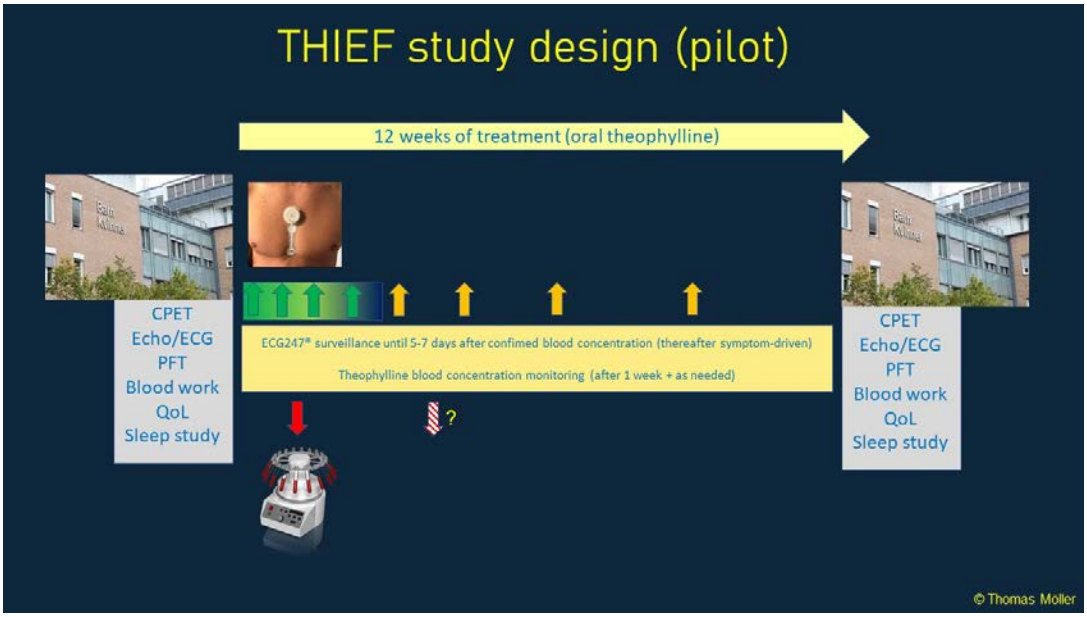
Drug regimen / adjustments:

After inclusion visit, the participant starts on oral study medication (theophylline depot tablets 200mg, start dose 200mg bid). In case of baseline bilirubin above 1.5 the upper normal limit, the start dose is 100 mg BID).

After 3-5 days, the participant visits the family physician or a nearby hospital laboratory to collect a blood sample 4-6 hours after drug intake which is shipped to OUS for analysis (serum concentration of theophylline, creatinine, ALAT, bilirubin). For details of sample handling and shipment see section 10.2 appendix 2: Clinical Laboratory Tests.
Target concentration of theophylline during study period is 30-80 µmol/Liter (4-6 hours after intake). Dose adjustments, if needed, are made by a physician at the research unit in collaboration with the PI. Dose increase or decrease depending on serum concentration by 100mg steps up or down, i.e., from 200mg bid to either 100mg bid or 300mg bid. A dose reduction from 100 mg BID will be 100 mg OD. Any dosing changes have to followed by repeat blood work after 3-5 days. For dose modification algorithm see section 6.5.

Data Monitoring/Other Committee: No

1.2. Schema


THIEF study design (pilot)
12 weeks of treatment (oral theophylline)
CPET
Echo/ECG
PFT
Blood work
QoL
Sleep study
ECG247® surveillance until 5-7 days after confimed blood concentration (thereafter symptom-driven)
Theophylline blood concentration monitoring (after 1 week + as needed)
?
CPET
Echo/ECG
PFT
Blood work
QoL
Sleep study
© Thomas Møller

1.3. Schedule of Activities (SoA)

Procedure	Screening (up to 28 days before Day 1)	Baseline Assessment		Intervention Period [Days or Weeks, etc.]								E/D	Follow-up (12-15 weeks after treatment start)	Notes E/D = Early Discontinuation * = may be postponed 1-2 days until 1st workday
		Up to 4 days be-fore Day 1	-1	1	Day 2-4	Day 5*	Day 6-11	Day 12*	Week 3-12 (-15)					
Informed consent	X													
Inclusion and exclusion criteria	X	X												
Demography	X													
Full physical examination including height and weight	X													
Medical history (includes history of heart surgery and cardiac interventions, arrhythmia history)	X													
Quality of life assessment (SF-36, EQ-5D)		X											X	
Pregnancy test (WOCBP only)	X	X										X	X	
Echocardiography		X										X	X	
12-lead ECG	X	X										X	X	
Cardio-pulmonary exercise test		X											X	
Pulmonary function test (incl. DLCO)		X											X	
Screening laboratory tests	X***													
Follow-up laboratory tests (include liver enzymes and renal function)		X				X		X**				X	X	** only if dose adjustment after day 5 theophylline conc.

Procedure	Screening (up to 28 days before Day 1)	Baseline Assessment		Intervention Period [Days or Weeks, etc.]								E/D	Follow-up (12-15 weeks after treatment start)	Notes E/D = Early Discontinuation * = may be postponed 1-2 days until 1st workday
		Up to 4 days be-fore Day 1	-1	1	Day 2-4	Day 5*	Day 6-11	Day 12*	Week 3-12 (-15)					
Blood sample for theophylline serum concentration (4-6 hours after intake)						X		X**				X		
Vital signs		X										X	X	
ECG home device instruction (ECG247®)		X												
Home-based ECG (review of online stored ECG readings and alarms)		X	X	X	X	X	X	Y	Y					X = daily/continuously (incl. 5 days after dose adjustment) Y= symptom-dependent
Home based sleep study – instruction and equipment delivery* (1 day loan)			X	X									X	
Oral treatment with Theophylline (Theo-Dur®)				←═══════════→										
AE review (weekly phone call from trial staff during intervention phase)		X		←═══════════→										
Unsolicited AEs		X		←═══════════→								X	X	See Appendix 3 for definitions Consider separate tables for days with multiple assessments
SAE review		X		←═══════════→								X	X	

Procedure	Screening (up to 28 days before Day 1)	Baseline Assessment		Intervention Period [Days or Weeks, etc.]								E/D	Follow-up (12-15 weeks after treatment start)	Notes E/D = Early Discontinuation * = may be postponed 1-2 days until 1st workday
		Up to 4 days be-fore Day 1	-1	1	Day 2-4	Day 5*	Day 6-11	Day 12*	Week 3-12 (-15)					
Concomitant medication review		X		←═══════════════════════→								X	X	

*** To avoid futile long-distance travel due to screening failure by laboratory results, samples for screening lab work might be collected locally and shipped to the study centre up to 28 days before screening visit and repeated on the day of visit if informed consent has been signed previously.

2. Introduction

Since the 1970's, the development of open heart surgery has allowed patients with the most complicated congenital heart malformations to survive into adulthood (6). Patients with univentricular heart malformations do not have two heart chambers supporting a normal circulation with two circuits. Instead, a series of heart surgery interventions create a so-called Fontan circulation, which is a common palliative surgical solution to a diversity of univentricular congenital heart defects. The surgical Fontan pathway leaves the patients with a single pumping heart chamber and a passive lung perfusion which powered by elevated central venous pressure. Due to improved perioperative and long-term survival, an increasing number of patients with Fontan circulation reach adulthood(7).

One of the major problems of the Fontan circulation is the very limited ability to augment cardiac output(8). Follow-up studies in these patients shows low aerobic exercise capacity compared to healthy individuals already during childhood(9-11). Furthermore, an inevitable decline of exercise capacity starts in adolescence or early adulthood (12). Exercise capacity in this patient group is closely linked to and predicts quality of life(13, 14).

Another long-term consequence is part of the complex entity of a failing Fontan circulation, which encloses heart failure symptoms, liver fibrosis and cirrhosis, protein-losing enteropathy, plastic bronchitis, immunodeficiency, and thromboembolic events(15, 16). The main limiting factors of exercise capacity and the factors responsible for late failure of the Fontan circulation are limitation of transpulmonary blood flow, resistance in the pulmonary vessels and diastolic function of the single ventricle(16, 17). Furthermore, a recent study has demonstrated a large proportion of adults with Fontan circulation showing sleep-disordered breathing which potentially impacts negatively on pulmonary vascular resistance(18, 19). Other factors contributing to the eventual failing of the Fontan circulation are:

1. Impaired heart rate response to exercise (chronotropic incompetence)(20).
2. Physical deconditioning of the patient with weakening of respiratory musculature (i.e. muscular diaphragm) and less effective inspiratory forces supporting venous blood return(21-23).
3. Reduced pulmonary function, decrease in respiratory efficiency on the alveolar and capillary level(24-27).
4. Neuro-humoral and inflammatory activation(28-31).

The final treatment for survivors of Fontan surgery is heart transplantation. However, as adult recipient candidates, patients with complex congenital heart disease have to compete with other recipient groups with less organ complications and better transplantation outcomes. Consequently, a significant research effort during the last decade has done to find therapeutic options to improve physical and cardiac function in Fontan patients when no further surgical improvement of the palliative circulation is possible. Non-surgical options would be pharmacological, skeletal and/or respiratory muscle training(32-35) or mechanical circulatory assist devices(36, 37).

2.1. Study Rationale

Our study aims to investigate the short-term effect of oral treatment with theophylline on exercise capacity, health-related quality of life, cardiac function and respiratory function in clinically stable adolescent Fontan patients who are not treated with sildenafil, bosentan or any other specific pulmonary vasodilator. The effects of theophylline, like other xanthine derivates, match in a remarkable way several pathophysiological mechanisms of Fontan failure:

1. Pulmonary vasodilation(38, 39)
2. Positive (inotrop) effect on myocardial contractility(40, 41)
3. Adenosine antagonism(42, 43)
4. Positive effect on contractility of the muscular diaphragm(44-46)
5. Increased renal perfusion(47, 48)
6. Anti-inflammatory effect(49-51)
7. Reduction of apnea/hypopnea episodes(52)

We have reviewed previous published data on methylxanthine effects in heart failure and other comparable cardiovascular conditions i.e., with elevated pulmonary vascular pressure. Parker et al. found in their experimental study in nine heart failure patients that theophylline ethylene diamine (aminophylline) reduces markedly the pressures in the right heart and pulmonary circulation, and theophylline increases cardiac output (62). Al-Damluji et al. demonstrated that a single oral dose of theophylline given to nine patients with chronic heart failure increased cardiac index and systemic arterial pressure, whereas left ventricular filling pressure and mean right atrial pressures fell (57). All of these representing favorable hemodynamic effects. Murphy et al. studied the effects of aminophylline in 28 patients with elevated pulmonary vascular pressures due to left heart disease (63). They demonstrated a positive inotropic effect documented by a decrease in left ventricular filling pressures and simultaneous increase in the maximum rate of ventricular pressure rise (dP/dT).

In summary, experimental studies in comparable cardiac conditions have demonstrated favorable hemodynamic effects of methylxanthines, namely as positive inotropic effect and by lowering pulmonary vascular pressure.

Hence, theophylline, even if it is and old and well-proven drug, is an intriguing substance to study for its potential to improve performance of the Fontan circulation, and it has not been studied in this context before.

The primary endpoint oxygen uptake at anaerobic/ventilatory threshold (VO_2@VAT) is chosen as primary endpoint from submaximal cardio-respiratory exercise parameters because it is representative of the circulatory part of cardiorespiratory fitness. Thereby VO_2@VAT measures pharmacologically achieved improvements of circulatory reserve with no regard if the participant achieves maximum exhaustion during cardiopulmonary exercise test.

2.2. Background

Through the last two decades pharmacological studies to improve performance in the Fontan circulation for patients' benefit have investigated effects of substances that are dilatators of the pulmonary vascular bed like the phosphodiesterase inhibitor sildenafil, and the endothelin antagonist bosentan(53).

Oral sildenafil has repeatedly been shown to improve both respiratory efficiency and exercise capacity in Fontan patients(54, 55). Results from studies with bosentan are more conflicting. A Dutch study failed to show an effect on exercise capacity(56), whereas a Danish study has proven a significant, but minor improvement of exercise capacity and functional class(57). Even if the effect of both drugs on exercise capacity is small (sildenafil) or uncertain (bosentan) and the treatment is expensive, they are currently the only pharmacological treatment options. Long-term beneficial effects of either of the two drugs on transplant-free survival are unknown. Most international centers are using bosentan, sildenafil or a combination in the treatment of Fontan patients of all ages when functional decline or failing of the Fontan circulation occurs. Cheaper and more effective pharmacological treatment strategies are still to be found.

The xanthine derivates aminophylline (intravenously) and theophylline (orally) have been used for decades in the treatment of obstructive pulmonary disease, either in the acute or the chronic phase(50). The main cellular mechanism of xanthine derivates leading to bronchodilation are still unknown. Xanthine derivates have several others effects that contribute to their positive impact not only on airway obstruction but also on the heart, the circulation and respiration (43). Due to the diverse and beneficial circulatory effects, the old drug theophylline recently has gained attention in treatment of heart failure and other cardiac disease(49, 58, 59).

The spectrum of effect mechanisms of theophylline matches remarkably with the different aspects of the limitation and/or eventual failure of the Fontan circulation. We therefore hypothesize that theophylline might have a positive effect on quality of life, exercise capacity, cardiac and pulmonary function in patients with a Fontan circulation. As theophylline has been used for many decades, pharmacokinetic, adverse effects, toxicology and safety profiles are well known(50).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of theophylline may be found in the Summary of Product Characteristics for Theo-Dur® 200/300 mg (https://www.legemiddelsok.no/_layouts/15/Preparatomtaler/Spc/0000-06607.pdf).

2.3.1. Risk Assessment

The theophylline-derived baseline heart rate increase and the risk of arrhythmia due to intoxication warrants special attention towards the proarrhythmic risk in patients with congenital heart disease. However, accelerated AV-node conduction due to theophylline has been associated with beneficial effects on bradycardia of different genesis and atrial fibrillation with slow ventricular rate (59). In an unselected hospitalized sample of 100 patients, Bittar & Friedman reviewed signs of arrhythmia in the ECG in relationship to theophylline serum concentration (60). Serum concentration was the strongest predictor of arrhythmia with atrial ectopic tachycardia being the predominant type of arrhythmia. No concomitant ventricular ectopy was found.

Treatment studies and experimental studies using theophylline in other heart disease populations with assumed comparable arrhythmic vulnerability have been published. Javaheri et al. treated 15 males with decompensated heart failure with reduced ejection fraction and sleep-disordered breathing with oral theophylline for five days. Theophylline trough concentration during treatment was 11±2 mcg/L with no difference in ventricular arrhythmia in terms of frequency of isolated

ventricular depolarizations, couplets during sleep or numbers of episodes of ventricular tachycardia defined as three or more premature ventricular beats in a row. (52). One of the patients in this study encountered supraventricular tachycardia with theophylline concentration in therapeutic range (8.6 mcg/L). Al-Damluji et al. studied the effects of a single intravenous dose of 600 mg theophylline in nine patients with chronic left ventricular failure (61). Seven patients had no changes to their heart rhythm. One patient in this study, with previous episodes of ventricular tachycardia before the study enrollment, had a non-sustained episode of ventricular tachycardia. This patient also had a toxic level of theophylline concentration. Andreas et l. studied the effects of intravenous theophylline in a double-blinded placebo-controlled study in eleven heart failure patients compared to both heart failure patients and healthy volunteers. They observed no change in heart rate in the theophylline / heart failure group and no arrhythmia episodes were reported (58). In a case-control study by Huerta et al. investigating the risk of arrhythmias due to different respiratory medications, ventricular arrhythmias were not associated with theophylline use, by short term use of theophylline was weakly associated with atrial fibrillation and supraventricular tachycardia (62). This study was conducted in non-cardiac patients and all arrhythmia types were also associated with steroid use and beta-adrenoreceptors.

The reduced elimination of theophylline shown in patients with chronic congestive heart failure is assumed to be related to liver function and galactose elimination capacity (63), which indicate cautious theophylline dosage in individuals with Fontan circulation and varying degrees of Fontan-associated liver disease. Hence, the first clinical trial with a new drug in this patient group should probably be performed in young adult individuals before Fontan-related organ complications, especially Fontan-associated liver disease, become more prevalent during adulthood (64).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (oral theophylline treatment)		
Clinical risks Side-effects from theophylline without overdosage and serum concentration within therapeutic limits: - Mild side-effects: tremor, headache, gastrointestinal disturbances (nausea, vomiting, anorexia) Moderate side-effects: eczema, urticaria Severe: new-onset atrial or ventricular tachyarrhythmia, in particular atrial ectopic	Side effects, toxicity and drug-drug-interactions according to SmPC (Preparatomtale) for Theo-Dur® 200/300 mg, section 4.8, 4.9 and 4.5 respectively. Risk consideration during pregnancy according to SmPC (Preparatomtale) for Theo-Dur® 200/300 mg, section 4.6.	Mild/moderate side-effects: Report to clinical research ward for children for consideration of actions by supervising physician (pediatric/adult). Severe side-effects: ECG home monitoring (as per schedule and symptom dependent), ECG review by

tachycardia (see section 7.1.2) Risk of increased toxicity or overdosage despite stable dose due to individual factors: - reduced theophylline clearance (heart failure) - liver disease (Fontan-associated) - viral infection/fever - hypokalemia due to coadministration of high-dose beta2-agonists in case of severe bronchial asthma - electro-convulsive treatment - hyperthyroidism - severe hypertension - interaction with other medication which increases serum concentration of theophylline, i.e., cimetidine, chinoline derivates like enoxacin, ciprofloxacin, perfloxacin, viloxazin, makrolid antibiotics like erytromycin, troleandomycin, allopurinol, propranolol, disulfiram, isoniazid, oral contraconceptives, flu vaccine, mexiletine, nifedipine, norfloxacine, ranitidin, tiabendazol, verapamil, fluvoxamine. Effects due to theophylline overdosage before serum concentration above therapeutic limit is detected: - seizures		team of supervising cardiologists (pediatric/adult). Serum concentration monitoring of theophylline, with a target concentration range well below the levels where tachyarrhythmias are most frequently reported. Unexpected toxicity and interactions: - Grading of Fontan-associated liver disease as per inclusion assessment, exclusion from study due to severe liver disease according to exclusion criteria - Report of viral/bacterial infections with fever to clinical research ward for children (decision of theophylline concentration monitoring by team of supervising cardiologists) - Written instruction to report/discuss with clinical research ward for children any current or intended other medical therapies during treatment phase - Written information about diminished effect of theophylline from intake of St John's-wort (Johannesurt, Hypericum perforatum)

		Overdosage prevention and handling: -low starting dose (200mg BID), theophylline serum concentration monitoring as per schedule and symptom-dependent - written information to general practitioner (fastlege) about study participation and symptoms of theophylline overdosage.
Study Procedures		
Non-clinical risks Risk of accidents during transportation to study related visits at hospital or laboratory		Minimizing the number of study-related visits
Clinical risks Risk of injury during cardiopulmonary exercise testing (CPET)	CPET is generally considered a safe procedure with < 5 adverse events per 100 000 tests(65)	Test supervision by experienced test leader and physician. Use of ergometer bicycle as exercise method
Other		
Non-clinical risks Risk of physical harm by misuse of ECG device is considered negligible.		

2.3.2. Benefit Assessment

Potential benefits for the patients according to main effects of the drug are to be explored by the study, but presumably they include better exercise tolerance and an improved general experience of physical well-being.

Experimental studies in comparable cardiac conditions have demonstrated favorable hemodynamic effects of methylxanthines, namely as positive inotropic effect and by lowering pulmonary vascular pressure.

For patients with univentricular heart disease and Fontan-type palliation the age span between 16 and 25 years of age corresponds to the most appropriate period in life for a first

trial of a new drug in this patient group. Impaired cardiorespiratory fitness (CRF) (potentially improved by theophylline) is a common experience in patients with Fontan circulation of all ages (11, 12). However, the subjective experience of being very different from peers starts in teenage years, and the gap between the CRF of patients and healthy peers only increases with impact on mental health and quality of life (13, 66). Hence the teenage years would be a good time to be able to initiate pharmacological treatment intended to improve CRF. And even if 16 years means to be minor in terms of clinical trials, the definition of an adult patient with full control of his/her medical treatment starts at 16 years of age in Norway.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with oral theophylline treatment are justified by the anticipated benefits that may be afforded to participants with Fontan circulation.

3. Objectives, endpoints and estimands

Objectives	Estimands and Endpoints
Primary	
• To investigate feasibility and safety of a 12 weeks treatment study design with remote dosage titration and handhold heart rhythm monitoring during treatment phase	Endpoints: • Frequency of treatment emerged AE/SAE • Freedom from participant dropout based on tolerability of the study intervention • Number of participants requiring dose reduction after first serum concentration assessment • Freedom of arrhythmogenic side effects of the study treatment leading to patient dropout
Primary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on exercise capacity in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation.	Estimand: • Circulatory reserve during exercise Endpoint: • Difference in oxygen uptake at anaerobic/ventilatory threshold pre/post treatment.
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment with theophylline on quality of life in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation.	Estimand: • Health-related quality of life Endpoint: • Difference in total scores from SF-36 and EQ-5D questionnaires pre/post treatment
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment on cardiac performance in adolescents	Estimand • Cardiac performance at rest

aged 16-25 years with univentricular congenital heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	Endpoint • Difference in ventricular function as assessed by echocardiography at rest pre/post treatment
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment on respiratory function including diffusion capacity in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	Estimand: • Pulmonary function Endpoint: • Difference in diffusion capacity pre/post treatment
Secondary	
• To provide an estimate of the effect size of 12 weeks of oral treatment on sleep disordered breathing in adolescents aged 16-25 years with univentricular congenital heart disease and Fontan circulation currently not treated with pulmonary vasodilators.	Estimand • Sleep apnea Endpoint • Change in Apnea Hypopnea Index during home-based sleep study pre-/post-treatment

4. Study Design

4.1. Overall Design

Single-group uncontrolled single-center open-label treatment study in adolescents (age 16-25 years) with univentricular congenital heart defects surgically palliated with a Fontan-type operation. Inclusion of eligible patients from inpatient and outpatient contacts at participating departments at Oslo University Hospital Rikshospitalet.
Study inclusion visit, drug treatment, remote dose adjustment, heart rhythm monitoring, and final post-treatment assessment study visit will be performed at the clinical research ward for children, Division of Paediatric and Adolescent Medicine.

Dose adjustment decisions and heart rhythm monitoring will be effectuated by a joint group of associated specialists (pediatric cardiology, cardiology) with continuous service through the entire study period.

Study duration: approximately 18 months (depending on inclusion progress, from inclusion of first participant until final visit of last enrolled participant)

Individual treatment duration: minimum 12 weeks, maximum 15 weeks or until final study visit.

Visit frequency: two study visits, at inclusion and at end of treatment period (earliest after 12 weeks of treatment and latest after 15 weeks of treatment).

Number of Participants: Ten participants of both sexes will be enrolled and invited to the study inclusion visit to achieve an intervention group of 10 individuals starting the oral treatment. In terms of being a pilot study, the study will also help to estimate the expected fractions of evaluable and non-evaluable participant in a subsequent full scale randomized clinical trial. Evaluability means the participant absolving all included study tests during inclusion and final study visit and completing scheduled dosage control and ECG monitoring tasks.

Note: "Enrolled" means a participant's or his/her legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Health measurement / observation:

At inclusion and final visit:

- Demographics, biometric data, medical history
- Quality of life assessment by questionnaire (SF-36, EQ-5D)
- Echocardiography for cardiac function assessment
- Pulmonary function test incl. diffusion capacity
- Cardiopulmonary exercise test (bicycle ergometer)
- Home-based polysomnography

During treatment phase:

- Dosage monitoring by analysis of theophylline concentration in blood sample (obtained locally) in addition to analysis of liver and renal parameters (ALT, bilirubin, creatinine), repeated on indication (after dose adjustment, in case of arrhythmic events)
- Treatment compliance and AE monitoring by symptom report in electronic participant log book in ViedocMe (part of the eCRF-database)
- ECG-monitoring (rhythm storage at least every hour) by tape-on ECG-device (ECG247®) connected to via smartphone app to an online database with 24/7 accessibility for medical monitor (5).
    - Starting from baseline visit during early intervention phase until 5-7 days after therapeutic concentration is achieved, the participant will continuously use the ECG247 device. In case of symptoms (palpitations or other arrhythmia-suspect symptoms), the participant will be able to notify the medical monitor (cardiologist) for immediate review of ECG readings.
    - After cessation of continuous ECG-monitoring, the participant will be equipped with additional ECG-tapes for symptom-initiated ECG-readings and contact with medical monitor as needed.

Drug regimen / adjustments:

After inclusion visit, the participant starts on oral study medication (theophylline depot tablets 200mg, start dose 200mg bid). In case of baseline bilirubin above 1.5 the upper normal limit, the start dose is 100 mg BID).

After 3-5 working days, the participant visits the family physician or a nearby hospital laboratory to collect a blood sample 4-6 hours after drug intake which is shipped to OUS for analysis (serum concentration of theophylline, creatinine, ALAT, bilirubin). Target concentration of theophylline during study period is 30-80 µmol/Liter. Dose adjustments, if needed, are made by a physician at the research unit in collaboration with the PI. Dose increase or decrease depending on serum concentration and drug tolerance by 100 mg steps up or down, i.e., from 200mg bid to either 100mg bid or 300mg bid (see also algorithm in section 6.5 Dose Modification). Any dosing change has to be followed by repeat blood work after 3-5 days and renewed review of theophylline concentration. A dose reduction from 100 mg BID will be 100 mg OD.

Data Monitoring/Other Committee:

Data Monitoring will be effectuated by Clinical Trials Unit at Oslo University Hospital Research Support.

A safety monitoring committee (see section 10.1.5 committee structure) consists of a patient representative and to external specialists in adult cardiology and pediatric medicine (committee leader) respectively. The safety monitoring committee is assigned for general safety discussions regarding study protocol, planning and trial intervention. The committee has no continuous participant monitoring tasks, but serves as a consultant for the medical monitors during trial execution in case of AE/SAE/SUSAR and the need to consider participant exclusion or trial termination.

4.2. Scientific Rationale for Study Design

Xanthine derivates have several others effects that contribute to their positive impact not only on airway obstruction but also on the heart, the circulation and respiration (43). Due to the diverse and beneficial circulatory effects, the old drug theophylline recently has gained attention in treatment of heart failure and other cardiac disease(49, 58, 59).

The spectrum of effect mechanisms of theophylline matches remarkably with the different aspects of the limitation and/or eventual failure of the Fontan circulation. We therefore hypothesize that theophylline might have a positive effect on exercise capacity, health-related quality of life, cardiac and respiratory function in patients with a Fontan circulation.

Our study aims to investigate the short-term effect of oral treatment with theophylline on exercise capacity, health-related quality of life, cardiac function and respiratory function in clinically stable adolescent Fontan patients who are not treated with sildenafil, bosentan or any other specific pulmonary vasodilator. The effects of theophylline, like other xanthine derivates, match in a remarkable way several pathophysiological mechanisms of Fontan failure. Furthermore, a recent study has demonstrated a large proportion of adults with Fontan circulation showing sleep-disordered breathing which potentially impacts negatively on pulmonary vascular resistance(18, 19). Potential beneficial effects of theophylline in the setting of Fontan circulation are:

1. Pulmonary vasodilation(38, 39)
2. Positive (inotrop) effect on myocardial contractility(40, 41)
3. Adenosine antagonism(42, 43)
4. Positive effect on contractility of the muscular diaphragm(44-46)
5. Increased renal perfusion(47, 48)
6. Anti-inflammatory effect(49-51)
7. Reduction of apnea/hypopnea episodes(52)

Hence, theophylline, even if it is and old and well-proven drug, is an intriguing substance to study for its potential to improve performance of the Fontan circulation, and it has not been studied in this context before.

The difference in VO_2@VAT before/after treatment is chosen as primary endpoint from submaximal cardio-respiratory exercise parameters because it represents the circulatory part of cardiorespiratory fitness. Thereby VO_2@VAT measures pharmacologically achieved improvements of circulatory reserve with no regard if the participant achieves maximum exhaustion during cardiopulmonary exercise test or not.

Secondary endpoints are assessments either of beneficial effects of increased cardio-circulatory reserve on subjective well-being (health-related quality of life) or of beneficial effects of theophylline on other organ systems (lungs/airways, kidneys, musculature).

The study aims to study theophylline effects in the Fontan circulation, and hence a non-Fontan control group would not add to study results or scientific knowledge gain.

The participants minimum age was chosen by the required age to provide informed consent and the lower age limit of adult quality-of-life assessment instruments. For patients with univentricular heart disease and Fontan-type palliation the age span between 16 and 25 years of age corresponds

to the most appropriate period in life for a first trial of a new drug in this patient group. Impaired cardiorespiratory fitness (CRF) (potentially improved by theophylline) is a common experience in patients with Fontan circulation of all ages (11, 12). However, the subjective experience of being very different from peers starts in teenage years, and the gap between the CRF of patients and healthy peers only increases with impact on mental health and quality of life (13, 66). Hence the teenage years would be a good time to be able to initiate pharmacological treatment intended to improve CRF. And even if 16 years means to be minor in terms of clinical trials, the definition of an adult patient with full control of his/her medical treatment starts at 16 years of age in Norway.

On the other side, the first clinical trial with a new drug in this patient group should probably be performed in young adult individuals before Fontan-related organ complications, especially Fontan-associated liver disease, become more prevalent during adulthood (64). Thus, the maximum participant age was chosen to avoid interference by other Fontan-related organ involvement in older adults, and to enable study coordination through the pediatric clinical research unit.

The 1:1 ratio of male/female inclusion was chosen to avoid gender bias and to ensure that sex-related differences in theophylline metabolism would not distort study results (67).

The study results in terms of safety and efficacy will be compared to three comparable drugs that have been tested in previous clinical trials in this patient population, namely enalapril, sildenafil and bosentan. Hence, to enable a comparison of drug safety and effects between different drugs, the duration of our study intervention for 12 weeks was chosen by both clinical judgment and oriented towards duration of interventions in the previous comparable trials.

Enalapril: 10 weeks (Kouatli et.al. 1997) (68)

Sildenafil: 6 weeks (Goldberg et al. 2011) (54)

Bosentan: 14 weeks (Hebert et al. 2014) (57)

6 months (Schuuring et al. 2013) (56)

4.2.1. Participant Input into Design

4.3. Justification for Dose

According to the SmPC (Preparatomtale) for Theo-Dur® 200/300 mg, section 4.2, normal start dosage for adults is 300mg BID. However, a reduced start dosage of 200mg BID is recommended in case of liver disease or heart failure. As theophylline has not been tested specifically in individuals with Fontan circulation, one cannot rule out a higher risk of theophylline side effects in this population. Hence, a stat dosage of 200mg BID with concentration measurements and dose titration, if necessary, was chosen for this study.

4.4. End of Study Definition

The end of the study is defined as the date of last study related procedure in any participant which might be either a completed final study visit, or finishing of a post-treatment home-based polysomnography and return of equipment.

A participant is considered to have completed the study if he/she has completed all phases of the study including a completed final study visit and finishing of a post-treatment home-based polysomnography and return of equipment.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 16 to 25 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with univentricular congenital heart disease with a Fontan-type palliation
   a. Who are able to perform all diagnostic and monitoring procedures necessary during trial period, in particular being able to perform a symptom-limited cardiopulmonary exercise test on an upright ergometer bicycle.
   b. With available hepatic imaging results (ultrasound or magnetic resonance imaging) from less than 12 months before inclusion
   c. Without biochemical indications of severe liver disease or liver failure (se exclusion criteria) of more than mildly reduced kidney function.
   d. Considered and assessed eligible for administration of Theo-Dur® (theophylline) as specified in the SmPC.

Weight

3. Body mass index (BMI) within the range 18.5 – 34.9 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

4. Contraceptive use by women is not under any national / local regulations in Norway.

a. Male participants: no restrictions.
b. Female participants: female participants should have a negative pregnancy test at inclusion and they receive information prior to consent that onset of pregnancy during treatment period has to be reported to the study team and leads to exclusion. Acceptable methods of contraception are defined in section 10.4.1 and 10.4.2

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
   For participants < 18 years, all (both) parents or caregivers with parental responsibilities have to sign the consent form in addition to the participant.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current or previous (last 12 months) tachyarrhythmia which has been cause of medical investigation or hospitalization.
2. Heart rhythm during inclusion visit other than:
   - sinus rhythm or regular supraventricular rhythm (visible P-waves) regardless P-wave angle
   - nodal rhythm
   - isolated extra beats (supraventricular or ventricular) of a frequency considered clinically non-significant
3. Systemic hypertension (systolic or diastolic blood pressure above 95 percentile)
4. Biochemical signs of more than mild liver disease or liver failure indicated by one of the following:
   a. INR > 1.4 in the absence of warfarin treatment or treatment with direct oral anticoagulants,
   b. ALAT more than twice the upper normal limit
   c. Bilirubin more than twice the upper normal limit
5. Imaging signs from the recent 12 months indicating severe Fontan-associated liver disease, indicated by:
   a. Imaging findings that need further diagnostic work-up to rule out hepato-cellular carcinoma
6. Biochemical indication of more than mildly reduced kidney function indicated by:
   a. Creatinine > 150 µmol/L (male) or > 120 µmol/L (female)
7. Pregnancy
8. Inherited forms of galactose intolerance (Lapp lactase deficiency eller glucose-galactose malabsorption
9. Hypersensitivity to theophylline

Prior/Concomitant Therapy

10. Current treatment with pulmonary vasodilator medication (sildenafil, tadalafil, udenafil, bosentan, ambrisentan, macicentan, or any prostacyclin derivate)
11. Ongoing pharmacological treatment with the risk of drug-drug interactions. (Examples: cimetidine, chinoline derivates like enoxacin, ciprofloxacin, perfloxacin, viloxazin, makrolid antibiotics like erytromycin, troleandomycin, allopurinol, propranolol, disulfiram, isoniazid, oral contraconceptives, flu vaccine, mexiletine, nifedipine, norfloxacine, ranitidin, tiabendazol, verapamil, fluvoxamine,

carbamazepine, felodipine, phenobarbital, phenytoin, rifampicine, lithium, ketamine, glucagon)

Prior/Concurrent Clinical Study Experience

12. No restrictions

Diagnostic assessments

13. No restrictions

Other Exclusions

14. Pregnancy or breastfeeding

5.3. Lifestyle Considerations

If applicable, describe any of the lifestyle considerations (diet, smoking habits, alcohol, or recreational drug consumption etc.) that could be of relevance for the study and any restrictions during any of the study periods. For example, include a statement about exposure to sunlight for study interventions with photosensitivity potential.

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of any formulations containing St John's-wort (Johannesurt, Hypericum perforatum) from 14 days before the start of study intervention until after the final dose.

5.3.2. Caffeine, Alcohol, and Tobacco

1. No restrictions for use of caffeine or alcohol.
2. Participants who use tobacco products will be instructed to keep their level of tobacco use during treatment phase because of reduction of serum half-time in smokers and risk of overdosage in case of smoke cessation during study treatment phase.

5.3.3. Activity

No restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently examined during an inclusion and final visit or treated with the study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) by other than imaging criteria may be rescreened for a maximum of two times.

5.5. Criteria for Temporarily Delaying

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Treatment		
Intervention Name	Theophylline		
Type	Drug		
Dose Formulation	Tablet		
Unit Dose Strength(s)	200 mg		
Dosage Level(s)	200 mg BID start dose (in case of elevated bilirubin 100 mg BID)		
Route of Administration	Oral		
Use	experimental		
IMP and NIMP	IMP		
Sourcing	Provided centrally by the Sponsor		
Packaging and Labeling	Study drug will be provided in packages. Each package will be labeled as required per country requirement		
Aliases / drug names	Theo-Dur®		

	Teofyllin Aurora Medical®		

6.1.1. Medical Devices

1. Medical devices (not manufactured by or for Oslo University Hospital) provided for use in this study are:
   a. ECG247® (manufacturer: Appsens, Senterveien 30, 4790 Lillesand, Norway) (5) EC Conformity Certificate No. 10000366191.PA-NA-NOR Rev.0.0
2. Instructions for medical device use are provided in written form to every participant and available online at: https://ecg247.no/forbruker/bruk/
3. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the [Study Reference Manual or other specified location].

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label, No blinding at site level	*This is an open-label pilot study with no randomization.*

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed by a weekly participant log book review performed by the study nurse, and during each visit. Compliance deviations discovered by either log book entries or by study visit will be followed up and assessed by the study nurse in terms of direct questioning and by counting returned study medication at final visit. During the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

Compliance deviations will be reported by the study nurse to the medical monitor as soon as practically possible, but within maximum two working days. The medical monitor has to evaluate the assessed compliance. The medical monitor has to decide by clinical judgement if the study intervention can continue without affecting study outcome, or if study participation has to be discontinued.

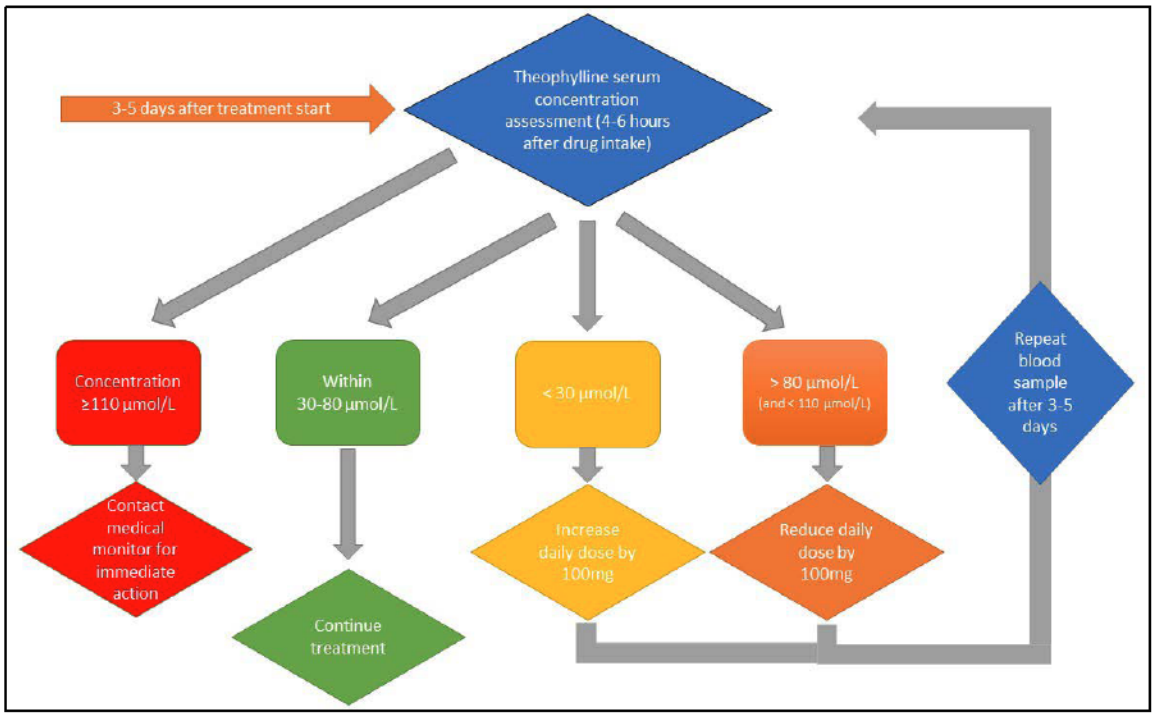
A record of the quantity of theophylline tablets dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

The decision to proceed to the next dose level of theophylline (either an increase or a decrease) will be made by the Study Team and the investigator based on serum concentration 4-6 hours after drug intake, safety, tolerability, and PK and pharmacodynamic data from SmPC (*Preparatomtale*).

Drug modification algorithm:

Target concentration of theophylline during study period is 30-80 µmol/Liter. Dose adjustments, if needed, are made by a physician at the research unit in collaboration with the PI. Dose increase or decrease depending on serum concentration and drug tolerance by 100mg steps up or down, i.e., from 200mg bid to either 100mg bid or 300mg bid (see also graphic algorithm). A dose reduction from 100 mg BID will be 100 mg OD. Any dosing change has to be followed by repeat blood work after 3-5 days and renewed review of theophylline concentration.



6.5.1. Retreatment Criteria

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

Continued access to theophylline treatment is possible on a strictly individual basis with approval of the participant after subjectively (health-related quality of life) or objectively (exercise capacity) improved health status. Continued off-label access to theophylline treatment is within responsibility of the participant's cardiologist and outside responsibility of the Study Team.

6.7. Treatment of Overdose / Intoxication

For this study, any dose of theophylline greater than twice the current treatment dosage within a 24-hour time period will be considered an overdose. Any serum concentration ≥ 110 µmol/Liter is considered suspicious of intoxication and should lead to immediate action and to verification (re-measurement) of serum concentration of theophylline.

Oslo University Hospital does recommend treatment for an overdose and/or intoxication in accordance with the SmPC (Preparatomtale).

In the event of an overdose and/or intoxication, the treating physician should:

- Contact the Medical Monitor immediately.

- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until theophylline concentration is within therapeutic range, or, in case of planned discontinuation, until theophylline can no longer be detected systemically (after at least 2 days).
- Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study. Herbal supplements containing St John's-wort (Johannesurt, Hypericum perforatum) must not be used from 14 days before treatment until the end of treatment.

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, and Ibuprofen at doses of ≤ 800 mg/day are permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.8.1. Rescue Medicine

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Criteria for early termination of the trial

The trial will be terminated if any of the following criteria are fulfilled:

- New or emerging safety information affect the benefit/risk assessment of the clinical trial negatively
- Two or more participants have to stop study intervention due to liver chemistry stopping criteria
- Two or more participants have to stop study intervention due to arrhythmia and QTc stopping criteria

7.2. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study to be evaluated. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in section 5.1.4 (exclusion criteria) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.2.2. Arrhythmia and QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline heart rhythm and changes in QT interval corrected using Bazett's formula [QTcB]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the 12-channel hospital ECG printed at the time of inclusion or review of ECG readings obtained by 12-channel ECG or ECG247 device during intervention phase must be documented. Any new clinically relevant finding should be reported as an AE.

The following arrhythmic events during intervention phase will lead to termination of study intervention in a participant (immediate cessation of theophylline treatment), if practically possible with immediate blood sample for theophylline serum concentration assessment and clinical outpatient visit at OUS Rikshospitalet as soon as possible:

- Sustained non-sinus supraventricular or junctional tachycardia of any type (atrial flutter, atrial fibrillation, ectopic atrial tachycardia, atrioventricular node reentrant tachycardia, atrioventricular reentrant tachycardia) with resting atrial rate of 100 minute^{-1} or higher and disregarding ventricular rate
- Premature supraventricular or ventricular beats with significantly increased rate (extra beats per minute) or different occurrence pattern (i.e.bigemini) compared to baseline ECG recording and combined with symptoms or otherwise considered clinically relevant
- New onset non-sustained or sustained ventricular tachycardia
- Any syncopal or near-syncopal event in close timely relationship to a documented arrhythmia in ECG247 recordings or in 12-channel ECG fulfilling discontinuation criteria

7.2.3. Temporary Discontinuation

Not applicable

7.2.4. Rechallenge

Not applicable

7.2.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit or phone/video call should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.4. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls or SMS). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular and Respiratory systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the lungs and cardiovascular system.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.
- Electrocardiograms: Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.3. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- Laboratory tests with values considered clinically significantly abnormal during participation in the study (together with theophylline serum concentration assessment) or within 1 week after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual (https://labfag.no) and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.4. Pregnancy Testing

A pregnancy test from a urine sample is performed in females during the inclusion visit.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Oral theophylline is NOT considered to be a CNS-active intervention and therefore monitoring for suicidal ideation and behavior or any other unusual changes in behavior apart from usual attention by medical professionals is not required.

8.3. Adverse Events (Aes), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (Aes) and serious adverse events (SAEs) can be found in Appendix 3.

Aes will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all Aes OR Aes that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the oral theophylline treatment (see Section 7).

All events that might qualify for being considered as Ae or SAEs recorded by any team member of the trial team has to be forwarded to the team of Medical Monitors as soon as practically possible, at the latest within 24 hours. Events in minor participants should preferably be reported to the principal investigator with pediatric qualification, events in adult participants should preferably be reported initially to the Medical Monitor with adult cardiology qualification. The latter will then evaluate the report and forward to the principal investigator based on an individual judgement.

The method of recording, evaluating, and assessing causality of Aes and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

All Aes will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as Aes.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on Aes or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Aes and SAEs

Care will be taken not to introduce bias when detecting Aes and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

During intervention phase, a research nurse from the pediatric clinical research unit will call the participant every week for a short interview to detect AE/SAE. To detect solicited AE, the participant will specifically be asked about symptoms with potential relation to arrhythmia events (palpitations, syncopal/near-syncopal events).
Detection of Aes might happen by entries into the electronic participant log book (ViedocMe), or by phone call initiated by either the study nurse or the participant (or representative). Also, phone calls from a participant (or representative) to one of the investigators (study phone 1-3) has to be considered a potential Ae and it has to be evaluated accordingly.

During the first period of study intervention (for every participant until 5 days after last necessary dose adjustment), one of the medical monitors will at least every 48 hours review the ECG recording portal for heart rhythm monitoring (ECG247, see section 6.1.1) as long as any of the participants is under continuous rhythm monitoring with ECG247. After that period, the medical monitor will review the ECG recording portal upon notification from the research nurse if any participant has reported AE suspicious symptoms and been asked to reapply the ECG247 for recording.
Results from the ECG247 review will be entered into the eCRF. A copy of the ECG recordings which are the basis of the evaluation report, will be stored in the patient's hospital record together with the report itself.

8.3.3. Follow-up of Aes and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until follow-up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant's pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6. Cardiovascular and Death Events

Any negative change from initial heart rhythm in the 12 channel ECG (inclusion visit, see exclusion criteria) on home-based ECG-monitoring has to be reviewed by a study physician / medical monitor. Change from supraventricular rhythm to nodal rhythm or vice versa are considered habitual/normal.

Tachycardic arrhythmic events have to be considered either as AE's or SAE's depending on medical consequences (need for medical intervention or hospital admission, spontaneous resolution). Possible events are:

- Sustained or non-sustained atrial/supraventricular tachycardia of any kind (ectopic automatism, supraventricular/nodal reentry)
- Sustained or non-sustained ventricular tachycardia
- Supraventricular or ventricular extra beats with frequency considered clinically significant by medical monitor.

In case of any tachyarrhythmia events, cessation of study intervention has to be considered by a medical monitor.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Aes or SAEs

The following disease-related events (DREs) are common in participants with Fontan-type palliation of univentricular congenital heart disease and can be serious/life threatening:

- Heart failure
- Thromboembolism
- Non-tachycardic arrhythmic events
- Cerebral abscess

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within the intervention phase. These DREs will be monitored on a routine basis. See Section 10.1

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- Event onset within 24 hours after initiation of study treatment
- Event onset within 24 hours after dosage uptitration. The investigator considers that there is a reasonable possibility that the event was related to study intervention (i.e., preceding suspected or documented arrhythmia event).

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.9. Medical Device Deficiencies

Medical devices are not being provided for use in this study as the study intervention.

8.4. Pharmacokinetics

PK parameters are not evaluated in this study.

Pharmacodynamic parameters are not evaluated in this study.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Antibodies will not be evaluated in the study.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics OR Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study hypothesis is that the study intervention positively affects Estimands leading to statistically significant changes from pre-intervention to post-intervention in primary and secondary endpoint variables.

Effects size on primary and secondary endpoint variables will allow for group size calculation in a future randomized clinical trial.

9.2. Sample Size Determination

The group size in this pilot study has been set voluntarily.

9.3. Analysis Sets

Not applicable

9.4. Statistical Analyses

9.4.1. General Considerations

Simple paired sample comparison (parametric or non-parametric) will be applied. No further statistical analysis plan is designed due to small pilot sample size.

Two-sided tests will be used on a 5% level of significance.

9.4.2. Primary Endpoint(s)

Safety – freedom from intervention-related adverse events or discontinuation.

Not statistically analyzable.

Difference in oxygen uptake at anaerobic/ventilatory threshold pre/post treatment (ml/min/kg)

Analysis by paired sample Student t-test or non-parametric paired samples test as appropriate.

9.4.3. Secondary Endpoint(s)

Difference in total scores from SF-36 and EQ-5D questionnaires pre/post treatment

Difference in ventricular function as assessed by echocardiography at rest pre/post treatment

Difference in diffusion capacity pre/post treatment

Change in Apnea Hypopnea Index during home-based sleep study pre-/post-treatment

Analysis of all secondary endpoint by paired sample Student t-test or non-parametric paired samples test as appropriate.

9.4.4. Tertiary/Exploratory Endpoint(s)

Not applicable

9.4.5. Safety Analysis

Not applicable

9.4.6. Other Analysis

Not applicable

9.5. Interim Analysis

Not applicable due to short intervention phase.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Identification of eligible patients:
  Eligible patients according to inclusion criteria will be identified by search in the patient registry on patients with congenital heart disease (all ages) at Oslo University Hospital, named BERTE. Only patients within ≤ 1 hour travel distance to the nearest hospital will be considered eligible. In case recruitment of patients who reside at long distance from the study site, the possibility of unplanned follow-up visits at the local hospital will be prepared by the study team by informing relevant health care providers. All regular study visits are performed at Oslo University Hospital.
  A search in the hospital's patient registry will involve access to identifiable information. Only lawful access by a medical monitor (pediatric or adult cariology) will be performed for eligibility identification purposes.
- Recruitment procedure:
  Eligible patients for study recruitment will be contacted by medical staff at Oslo University Hospital in different ways depending on previously planned inpatient or outpatient appointments:
  - Patients (caregivers for minors) with planned appointments within a short time (less than 3 months) will be recruited by oral information from a physician from the team of investigators at the time of their clinical appointment.
  - Patients (caregivers for minors) with no planned appointment in the near future will be contacted by phone. If the patient I generally interested in adjusting outpatient appointment schedule, an outpatient appointment will be offered for both clinical follow-up and for information / recruitment.
- The investigator or his/her representative will explain the nature of the study to the participant and for participants < 18 years also to their legally authorized representative and answer all questions regarding the study.
- Obtaining informed consent will be performed by study staff with no current involvement in the participants medical treatment (either physician [specialist in pediatric medicine] or research nurse
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative [in participants < 18 years defined as parents or caregivers will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

A safety monitoring committee consists of a patient representative and to external specialists in adult cardiology and pediatric medicine (committee leader) respectively. The safety monitoring committee is assigned for general safety discussion regarding study protocol, planning and trial intervention. The committee has no continuous participant monitoring tasks, but serves as a consultant for the medical monitors during trial execution in case of AE/SAE/SUSAR and the need to consider participant exclusion or trial termination.

A user/patient committee with three members is assigned for user communication and input during all study phases.

Due to small sample size and open-label non-randomized pilot study design with short intervention phase, no additional committees er assigned.

10.1.6. Early Safety Data Review AND/OR Committee

Due to small sample size and open-label non-randomized pilot study design with short intervention phase, no such review or committee is applicable.

10.1.7. Dissemination of Clinical Study Data

Study results will be published as scientific conference abstracts and as scientific manuscripts in peer-reviewed journals in an open-access-way of publishing.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- Guidance on completion of CRFs will be provided in study documents provided to the Clinical research ward for children.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan provided by the Clinical Trial Unit at OUH.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs and clinical trial master file, pertaining to the conduct of this study must be retained by the investigator for twenty-five years after study completion. Archiving of patient files / medical records will be executed according to Norwegian law (Pasientjournalloven). No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. After the archiving period, all personal data in relation to the study, and which are not part of the participant's medical record, shall be erased or made anonymous, cf. GDPR article 5 (1) and the Norwegian act on medical and health research § 38.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data verification document.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from

source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- The following data will be extracted from the participant's medical hospital record and transferred into the eCRF:
  - Diagnostic and anatomic details about the congenital cardiac disease before surgical treatment
  - Date and technical proceeding for previous heart surgery
  - Results from diagnostic liver assessment (both imaging and biochemical) from the last 12 months before study inclusion
  - Information about any heart rhythm disturbances, treated or untreated, from the last 12 months before study inclusion
  - Information about circumstances or previous test results which might fulfill any exclusion criterium (severe liver disease, systemic hypertension, inherited galactose intolerance, theophylline hypersensitivity)
  - Information about concomitant pharmacological treatment representing an exclusion criterium

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first screening of a patient meeting inclusion criteria during his/her clinical visit or hospital stay and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the central laboratory at Oslo University Hospital Rikshospitalet.
- Local laboratory results are only required in the event of suspected AE's or SAE's and the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Serum samples collected for theophylline concentration measurement will be stored at -20°C for 60 days for reanalysis purposes in case of AE/SAE and suspicion due to biochemical analysis failure and dosage error (69). There will be no establishment of a research biobank which would fall under national Norwegian rules regarding research biobanks.
- Handling of biological samples is in compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)
    - Both blood samples and urine samples are collected, a maximum of one sample of each type per occasion
    - Urine samples are discarded immediately after bedside pregnancy test or after biochemical and pharmacological analysis respectively according to trial protocol
    - The clinical trial does not involve the collection of existing archive samples
    - Samples will be collected either at OUS (inclusion and final visit), or at OUS or the closest facility (primary care physician or closest hospital laboratory) during treatment phase. Externally collected samples are shipped with routine biological sample shipment (postal transport or hospital-to-hospital delivery service) to OUS. Details for sample handling and shipment are given in a letter to the participants health care providers (appendix 2 to the ICF) in accordance with publicly available instructions (https://ous.labfag.no → Oslo universitetssykehus → Teofyllin).
    - All analyses will be processed within the Sponsor's organization (Oslo University Hospital). No samples are will be sent for further analysis from OUH to other institutions.
    - Samples will be marked with study ID and only trial personnel and laboratory personnel (by trial agreement) will have access to the samples
    - No biological samples will be stored beyond 60 days for any future use.

Table 1: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (karbamid)	Potassium (K)	Aspartate Aminotransferase (ASAT)	Total bilirubin
	Creatinine	Sodium (Na)	Alanine Aminotransferase (ALAT)	Total Protein
	Glucose, non-fasting	Calcium	Alkaline phosphatase[2]	INR
Routine Urinalysis	pH, glucose, protein, blood, ketones by dipstick			
Pregnancy testing	• Highly sensitive [urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]			
Other Screening Tests	None			

NOTES:

1 Details of liver chemistry stopping criteria and required actions and follow-up are given in Section [7.1.1 Liver Chemistry Stopping Criteria] and Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

2 If alkaline phosphatase is elevated, consider fractionating.

3 Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Aes and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited Aes include serious and non-serious Aes. • Potential unsolicited Aes may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/ parental /LAR's concern. Detailed information about reported unsolicited Aes will be collected by qualified site personnel and documented in the participant's records. • Unsolicited Aes that are not medically attended nor perceived as a concern by participant/participant's parent(s)/LAR(s) will be collected during interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit. • Solicited Aes are predefined local and systemic events for which the participant is specifically questioned.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are Aes. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Medical or scientific judgment should be exercised by a medical monitor in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Definition of suspected unexpected serious adverse reaction (SUSAR)

If an event is not an SAE per definition above, then it cannot be a SUSAR

SUSAR Definition

Adverse Reaction: all unwanted and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable Summary of Product characteristics (SmPC).

Suspected Unexpected Serious Adverse Reaction: Unexpected Adverse Reaction that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the medical monitor to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The medical monitor will then record all relevant AE/SAE information.
- It is **not** acceptable for the medical monitor to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The medical monitor will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The team of medical monitors will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The team of medical monitors is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The team of medical monitors will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The team of medical monitors will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the team of medical monitors **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the team of medical monitors has minimal information to include in the initial report to the Sponsor. However, it is very important that the team of medical monitors always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The team of medical monitors may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Aes and SAEs

- The team of medical monitors is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- For all reported events evaluated by a medical monitor, the medical monitor has to consider if a hospital visit is needed for further clarification of the nature of the event. The medical monitor will, if necessary, arrange for an outpatient visit to either the outpatient clinic of the pediatric or adult cardiology service at Oslo University Hospital Rikshospital for the following work day.
- If the participant reporting an event is considered by the medical monitor to need immediate medical attention, the medical monitor will arrange for an emergency outpatient visit to the pediatric or adult cardiology service at Oslo University Hospital Rikshospital or, if preferable due to travel distance, at the nearest qualified hospital.

- If a participant dies during participation in the study or during a recognized follow-up period, the team of medical monitors will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The team of medical monitors will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting are the medical monitors:
  For events in participants < 18 years of age:
  Thomas Möller MD PhD (contact details see page 2)
  For events in adult participants:
  Ola Gjesdal MD PhD (contact details see page 2)

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the team of medical monitors to complete and sign the SAE data collection tool within the designated reporting time frames.

- Contacts for SAE reporting can be found in https://legemiddelverket.no/english/pharmacovigilance.

10.3.6. Reporting of SUSAR

medical monitor will evaluate if a reported SAE also is a SUSAR, if so, the medical monitor will report the SUSAR to the Competent Authority through Eudravigilance (EV)

Sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible and in no case later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

Other SUSARs will be reported no later than 15 days after the incident.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Different pharmacokinetics of theophylline have not been demonstrated in pregnant women (70). The SmPC recommend close monitoring of serum theophylline concentrations during the third trimester and weighing of risk and benefits of theophylline treatment during pregnancy.

The scientific literature concerning risks of theophylline use during pregnancy has been reviewed in 2006 by Chambers (71). The author concluded that "although no significantly increased risk for major birth defects was noted with first trimester exposure to theophylline in any of the studies cited above, sample sizes in each study were insufficient to rule out anything but high relative risks for major birth defects overall or for any specific birth defect." Hence, even if the risk of major congenital defects and severe pregnancy events during the first trimester of pregnancy seem not to be elevated, the relatively limited available evidence still does not justify the conclusion that onset of pregnancy in study participants would be acceptable.

Therefore, pregnancy is considered being an exclusion criterium at recruitment visit. Onset of pregnancy during treatment phase is not advised. If pregnancy during treatment phase or final visit is diagnosed, the participant will be excluded from the study and theophylline treatment will be stopped.

10.4.1. Definitions

Usable contraceptive methods for sexually active women living with Fontan-circulation are:

a. Barrier method: condom, diaphragm.
b. Hormonal contraceptive: oral contraceptive (gestagen only), gestagen-containing IUD or subcutaneous implant.

c. Surgical sterilization

10.4.2. Contraception Guidance

Female participants who are not sexually active are informed about treatment risks related to pregnancy and the need of effective contraception in case of onset of sexual activity during treatment phase.
Female participants of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial. Women of child bearing potential (WOCBP) are defined as sexually active women between 15 and 45 years of age, meaning all eligible female participants as long as they are not considered non-fertile for medical reasons.

Acceptable contraceptive methods for WOCBP during study participation are hormonal contraception or previous sterilization.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Any excess of liver safety parameters during treatment phase or during the final visit has to be evaluated by the medical monitor. Recommended action is to repeat laboratory assessment 2-4 weeks after treatment cessation. If elevated laboratory results persist, liver imaging studies should be conducted in consultation with hepatology services (pediatric or adult as appropriate).

10.7. Appendix 7: Aes, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

10.8. Appendix 8: Country-specific Requirements

Not applicable.

10.9. Appendix 9: Abbreviations Delete appendix if not required.

AE	Adverse event
ALAT	Alanine-aminotransferase (enzyme)
ASAT	Aspartate-aminotransferase (enzyme)
bid	dosage twice daily
BMI	Body mass index
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case record file
CPET	Cardiopulmonary exercise test
DLCO	Diffusing capacity for carbon monoxide
DRE	Disease-related events
ECG	Electrocardiogram
ECG247	Heart rate and rhythm monitoring devise (see: https://ecg247.no)
eCRF	Electronic case record form
EQ-5D	European quality-of-life questionnaire with five domains
GCP	Good clinical practice
hCG	Human chorionic gonadotropin (hormone)
ICF	Informed consent form
IEC	Independent Ethics Committees
IMP	Investigational medicinal product
INR	International normalized ratio (for anticoagulation treatment assessment)
IRB	Institutional Review Boards
IUD	Intra-uterine diaphragm (contraception)
K	Potassium
LAR	Legally authorized representative
MCH	Mean corpuscular hemoglobin content (red blood cells)
MCV	Mean corpuscular volume (red blood cells)
Mg	Milligrams
MRI	Magnetic resonance imaging
Na	Sodium
NIMP	Non-investigational medicinal product

OUH	Oslo University Hospital
OUS	Oslo universitetssykehus (Norwegian term for OUH)
PI	Principal investigator
RBC	Red blood cell count
SAE	Serious adverse event
SF-36	Short form 36, quality-of-life questionnaire
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
VO_2@VAT	Oxygen uptake at anaerobic/ventilatory threshold
WBC	White blood cell count
WOCBP	Woman/women of child bearing potential

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01 (substantial modification: (Nov 04, 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

A decision in the study team was made to use an electronic log book solution for better monitoring of participant compliance and AE's. This decision was made after initial trial application authorization.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Signature page	Filled in correct contact details	Preliminary placeholders from protocol version 1 are replaced
Protocol Amendment Summary of Changes Table	A table and overview of amendment history has been added	Necessary change together with amendment no.1
1.1 Synopsis, Brief summary	Added information about electronic participant log book in ViedocMe (part of the eCRF database)	A decision in the study team was made to use an electronic log book solution. This decision was made after trial authorization.
4.1 Overall design	Added information about electronic participant log book in ViedocMe (part of the eCRF database)	A decision in the study team was made to use an electronic log book solution. This decision was made after trial authorization.
Whole document	Typographic and semantic errors and flaws including institutional name changes were corrected	(Non-substantial changes)

Amendment 02 (substantial modification: March 28, 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Initial screening visits of potential participants revealed frequent screening failure (6 out of 10 visits) due to biochemical exclusion criteria, namely elevated ammonia and/or mildly elevated INR in the absence of signs of moderate/severe liver disease by other biochemical (bilirubin,

ALT) or imaging findings (MRI or ultrasound). The intention behind liver-related exclusion criteria was to exclude participants with either potential hepato-cellular carcinoma or with severe Fontan-associated liver disease with significantly impaired synthesis or significantly increased theophylline toxicity.

Experiences with repeated screening failure, experiences with the initial three enrolled participants, and a focused review of available scientific literature resulted in the following considerations:

- Porto-systemic shunting of enteral venous blood to the systemic venous system leads to elevated ammonia and should probably be expected frequently late (> 10 years) after the Fontan operation (Takefuta 2021) (1). Hence ammonia is not suited to discriminate different degrees of hepatic involvement in Fontan patients.
- In a previous study of hepatic and cardiac function in Fontan patients, spontaneous INR had a median of 1.2 equivalent to the upper normal range (Camposilvan 2008) (2). A spontaneous INR above the upper normal limit (>1.2) is probably a too restrictive exclusion criteria in a Fontan population. In addition, the use of direct oral anti-coagulant drugs may cause slightly elevated INR in the absence of warfarin treatment (Ofek 2017) (3).
- Bilirubin has been shown to correlate with slow theophylline clearance in cirrhotic patients (Mangione 1978) (4). Even in the absence of elevated ammonia and severe liver disease, a theophylline concentration within therapeutic range was achieved by 2/3 participants on a low starting dose (200 mg BID) or even after dose reduction from initial dosage (100mg BID)

Other practical protocol, recruitment and consent issues that became obvious during the first screening visits and inclusions (see table).

Section # and Name	**Description of Change**	**Brief Rationale**
1.3 (Synopsis) 4.1 (Overall design) 6.5 (Dose modification)	Reduced starting dose of study drug depending on bilirubin level, and option to further reduce to OD depending on study drug concentration	Theophylline clearance has been demonstrated to correlate with bilirubin level, and 2/3 participants have achieved therapeutic theophylline concentrations on study drug dosage below recommended staring dose in adults
1.1 (Synopsis)	Removed mandatory gender ratio of 1:1	Both genders should be represented in study group, but no rationale for 1:1 existed
1.3 (Schedule of Activities)	Screening laboratory tests (more comprehensive compared to baseline and follow-up) might be collected locally and	Our study design has been shown to allow for safe participant monitoring independently of travel distance to the study center. To avoid futile long-

	shipped to the study centre up to 28 days before screening visit and repeated on the day of visit if informed consent has been signed previously.	distance travel due to screening failure by laboratory results.
1.4 (Schedule of Activities) 4.1 (Overall design)	Home-based ECG-monitoring device is started during baseline visit	Recording of baseline ECG-readings with the monitoring device for comparison during treatment monitoring
1.3 (Schedule of Activities)	A time interval of 1-3 days for completing baseline visit with polygraphy has been defined with subsequent start of study medication	Practical / logistical difficulties to always perform polygraphy during first night after baseline visit (device shipping and device turnover between participants)
5.1 (Inclusion criteria)	Rephrasing of general liver-related criteria	Defining of only severe Fontan-associated liver disease as safety issue during theophylline use (corresponding to bilirubin-dependent study drug start dose)
5.2 (Exclusion criteria)	The upper limit of acceptable INR has been altered.	Some elevation of INR in the absence of severe liver disease has been described in Fontan patients and in patients using direct oral anticoagulative drugs
5.2 (Exclusion criteria)	Liver imaging exclusion criteria has been rephrased as “Hepato-cellular-carcinoma (HCC)-suspect lesions” by liver imaging.	The imaging-related exclusion criteria of “nodules > 10 mm” by MRI or ultrasound images have been difficult to apply to imaging reports from individual patient files. We noted frequent descriptions of lesions below/above 10 mm with altered perfusion, but without a nodular/expansive structure.
5.2 (Exclusion criteria)	Ammonia has been removed from biochemical exclusion criteria	Disease-specific alterations in liver circulation in patients with Fontan circulation have led to screening failure in an unexpected high percentage of potential participants due to elevated ammonia levels in the absence of severe liver disease.

5.5 (Screening failures)	Re-screening permitted	A rescreening option with optimized blood work circumstances will improve recruitment of participants with otherwise no signs of severe liver disease.
10.4.2 (Contraception Guidance)	Absence of opposite gender sexual activity during study period has been explicitly defined as sufficient contraception.	Unnecessary use of oral contraception in female Fontan patients must be avoided due to risk of thromboembolism.

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