Final Study Report

Study Title: Safety and Efficacy of Patient Controlled Analgesia using the Sublingual Sufentanil Tablet System (SSTS) in a fast track rehabilitation program after Total Knee Arthroplasty.

EudraCT number: 2019-001232-59

Eudamed number: NA

Study protocol code: AGO/2019/002

ClinicalTrial.gov identifier: NCT04432428

Sponsor: *UZ Ghent*

National Coordinator/ Coordinating Investigator: Prof. Dr. P. Wouters

Funder: *Grunenthal*

Date of report: 16/03/2023

Name and signature Sponsor: University Hospital Ghent

Date signature Sponsor: ....16 MARCH 2023.....

Prof. dr. Patrick WOUTERS
DIENST VOOR ANESTHESIE
UNIVERSITAIR ZIEKENHUIS
De Pintelaan 185, 9000 Gent
Anesth.1-06495-11-100

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1. Introduction

The sufentanil sublingual tablet system (SSTS) is an innovative patient-controlled analgesia (PCA) device for the management of acute moderate to severe postoperative pain in hospital settings in adult patients. Phase III trials show that SSTS is not inferior to opioid-based Intravenous PCA, which is the current gold standard. In comparison to intravenous PCA systems however, the SSTS is non-invasive and imposes far less restrictions on patient mobility. These properties render it particularly suitable for clinical conditions where early mobilization is a key component of successful surgical outcome.

Total knee arthroplasty is one of the most common major procedures performed today with a significant impact on health care budgets. Fast track rehabilitation programmes are being developed to control hospitalization costs associated with this procedure. Interestingly, such pathway controlled fast track programs also appear to enhance functional recovery and to reduce complications. These beneficial effects are mainly attributed to the practice of rapid mobilization and early intensified physiotherapy which can only be achieved with effective analgesic techniques.

Current PCA techniques – predominantly morphine based - are the gold standard for this purpose but they involve intravenous access and a programmable computer system requiring close supervision. Reported shortcomings are systems failure leading to analgesic gaps, drug errors and restrictions in mobility since patients are tethered to IV poles. The SSTS may overcome these limitations because the opioid used, sufentanil, has a more predictable time of onset, the delivery system does not require programming, and the device does not limit patient's mobility. It retains the benefits of potent analgesia as well as patient empowerment and is particularly suited to target the analgesic effect precisely to the level required in physiotherapeutic sessions.

Previous studies evaluated SSTS in orthopedic and abdominal surgery in comparison to placebo or IV PCA but did not address analgesic efficacy during mobilization. The present study will test the hypothesis that SSTS is an efficient and safe analgesic technique allowing fast track rehabilitation after total knee arthroplasty in a prospective cohort design.

The study will focus on the efficiency of STSS which is defined as 75% or more of the treated patients proves NRS score less than 4 during 48 hours postoperatively, additionally to the basic pain treatment (paracetamol and NSAID).

2. Objectives of the study

The present study tests the hypothesis that SSTS is an efficient and safe analgesic technique allowing fast track rehabilitation after total knee arthroplasty in a prospective cohort design.

2.1 Primary objectives

Efficiency of SSTS which is defined as 75% or more of the treated patients proves NRS less than 4 during 48 hours postoperatively, additionally to the basic pain treatment (paracetamol and NSAID)

2.2 Secondary objectives

Safety of the SSTS based on the amount and type of side effects, classified conform NIH criteria (CTCAE) (National institute of health criteria (common terminology criteria for adverse events)) and the risk of causal relationship with the treatment

Level of analgesia during physiotherapy

3. Investigational Medicinal Product

Zalviso® : Cartridge with 40 tablets of sufentanil 15microgram

Each tablet for sublingual use contains 15 micrograms sufentanil (as citrate).

3.1 Producer

Grünenthal GmbH, Zieglerstr. 6 D-52078 Aachen, Germany

3.2 Distributor

Grünenthal GmbH, Zieglerstr. 6 D-52078 Aachen, Germany

3.3 Packaging

EU/1/15/1042/001 Zalviso 15 µg Sublingual tablet Sublingual use cartridge (PC) 40 (1 cartridge x 40) tablets

3.4 Administration

Zalviso is available as sublingual tablets containing 15 micrograms of sufentanil.

The tablets will only be administered on-site, where qualified personnel is available.

The patient places the Zalviso tablets under their tongue when needed using a special device. The device locks for 20 minutes after the patient has taken a tablet and does not allow the patient to take more than 3 doses in one hour. The device also uses an identifier so that only the patient who has been given a special thumb tag can release tablets. The tablets must be allowed to dissolve under the tongue and must not be chewed or swallowed. Treatment is continued over a period of 48 hours or if necessary up to 72 hours.

3.5 Labelling

Commercially available labeling; following particulars will be added on a type 2 label: sponsor, study reference code, investigator, study participant initials, study ID, date of administration, for clinical trial use only, direction for use

Ghent University hospital: labelling will be done by the study nurse, in the study office

Yperman hospital: labelling will be done in the hospital pharmacy, by a pharmacist

3.6 Storage conditions

Storage in the original package in order to protect from light, temperature between 15°C and 25°C

Ghent University hospital : – operating theatre, in a locked closet with temperature monitoring, accessible for staff members anesthesiology and study nurse
Yperman hospital – Hospital pharmacy with temperature monitoring, accessible for hospital pharmacists. Study nurse or collaborating anesthesiologist will pick up study medication.

4. Investigational Medical Device

NA

5. Study Protocol Summary

5.1 Inclusion criteria

We include patients between the age of 40 – 75 years, who are admitted for elective total knee arthroplasty, qualify for a fast track rehabilitation program with early mobilization and early hospital discharge, who understand the PCA principle and are capable to operate the SSTS device.

5.2 Exclusion criteria

Patients who have contra indications for anti-inflammatory drugs, a history of substance abuse, severe hepatic impairment (INR>1,5 and/or AST/ALT above x3 highest normal value), sleep apnea, severe chronic kidney disease (eGFR<30 mL/min/1.73 m2, severe and very severe COPD (GOLD III and IV), opioid tolerance (use of >15mg oral morphine equivalent per day within the past 3 months, chronic pain conditions necessitating gabapentinoids, steroids hypersensitivity to sufentanil, significant respiratory depression (need for outpatient supplemental oxygen therapy, are excluded. Patients planned for revision total knee arthroplasty or who participate in another clinical trial will also be excluded as well as patients who are pregnant or lactating.

5.3 Primary endpoint

Cumulative/total time when NRS<4 during 48 hours postoperatively

5.4 Secondary endpoints

- length of hospital stay
- nausea
- vomiting
- itching
- drowsiness
- constipation
- desaturation
- evaluation by health care workers (nurses, physiotherapists)
- evaluation by the patient
- consumption of study medication during study period for each patient

5.5 Procedures

Related to the study:

1. Study medication

Start administration medication at request of the patient or NRS≥4
T0 : 20 minutes after first use of PCA STSS at PACU
Stop administration medication : at 48 hours postoperatively, for comfort reasons it can be continued until 72 hours postoperatively

2. Pain responses (NRS scores)

every 30 minutes first hour after initiating of the study medication,
every hour between 1 and 6 hours
every 2 hours between 6 and 8 hours
every 4 hours starting from 8 hours till 48 hours postoperatively
every hour during exercises (by patient him/herself)

if NRS≥4 : repeat NRS after 20 minutes

3. Vital signs:

   Heart rate
   Blood pressures: systolic and diastolic
   Respiratory rate
   SaO2, without supplemental oxygen therapy

Assessment of oxygen saturation, respiratory rate and heart rate will occur every hour during the first six postoperative hours, then at 8 hours postoperatively, further every 4 hours

Blood pressure will be measured every 2 hours until 8 hours postoperatively and then every 4 hours postoperatively

During the physiotherapeutic exercises only the respiratory rate will be registered every hour.

4. Presence of nausea, vomiting, pruritus, dizziness, constipation

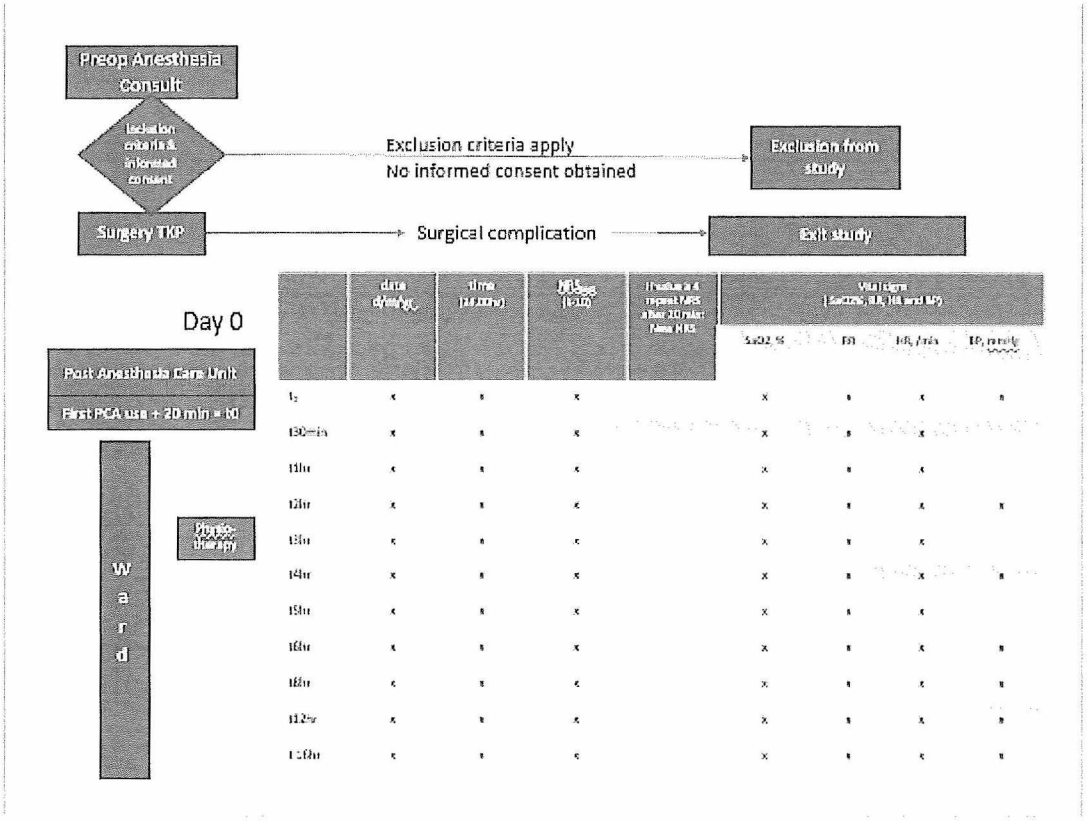
Assessment: once a day

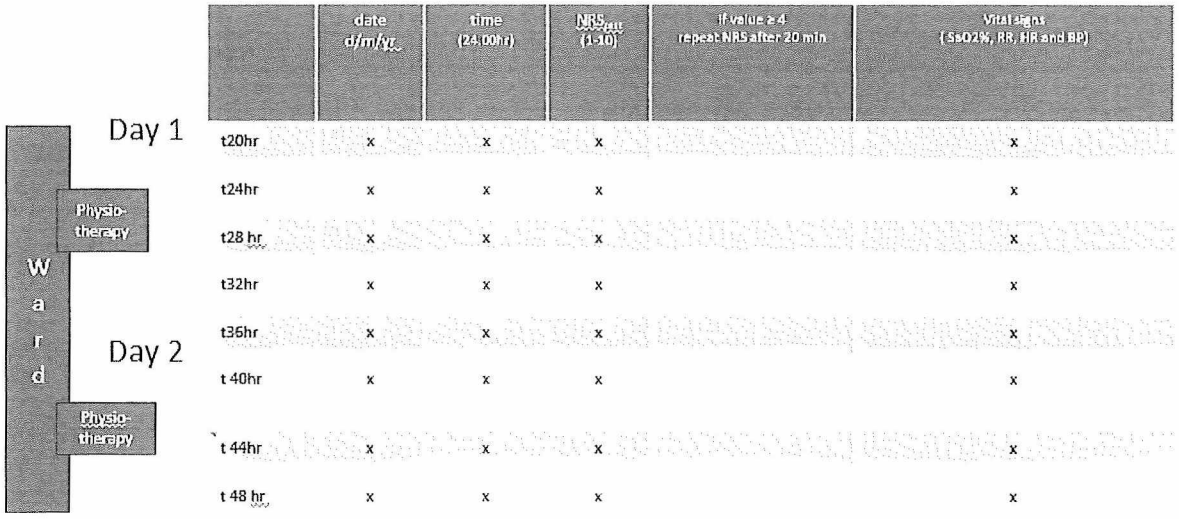
5. Patient satisfaction and satisfaction of health care workers (nurses and physiotherapists) using a questionnaire

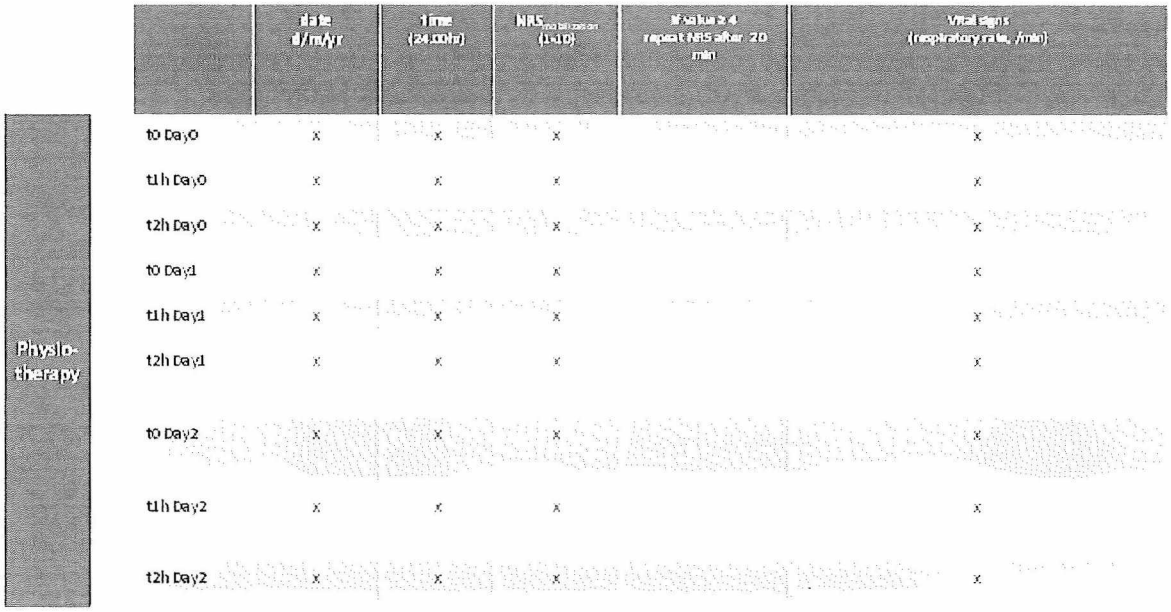
Evaluation by the patient : after discontinuation of study medication, uttermost before discharge.
Evaluation by health care workers (min 1 nurse and 1 physiotherapist) : after discontinuation of the study medication in each patient, uttermost 7 days after discontinuation

Unrelated to the study:

➔ Routine preoperative workup, intraoperative surveillance and postoperative clinical follow up according to local hospital policy for total knee replacement surgery.







	date d/m/yr	time (24.00hr)	NRS$_{mobilization}$ (1-10)	if value ≥ 4 repeat NRS after 20 min	Vital signs (respiratory rate, /min)
t0 Day0	x	x	x		x
t1h Day0	x	x	x		x
t2h Day0	x	x	x		x
t0 Day1	x	x	x		x
t1h Day1	x	x	x		x
t2h Day1	x	x	x		x
t0 Day2	x	x	x		x
t1h Day2	x	x	x		x
t2h Day2	x	x	x		x

5.6 Randomisation and blinding

Prospective Cohort Study
No randomization or blinding.

6. Study analysis

The study design contains only one treatment group (without a control group) with new form of administration of strong painkiller where the patient uses the device (PCA, or patient controlled analgesia).

The study will be conducted in 2 centers, with both centers recruiting the same number of patients.

The aim of the new treatment is to prepare patients for a quick discharge after knee surgery. This means that physiotherapy treatment has to be started sooner. This should be possible with the new treatment method pursuing better pain relief.

The target is achieved when a patient does not report twice consecutively a pain score > 4 and prepare for discharge within 48 hours after surgery with daily exercises.

The outcome will be considered as failure if the patient needs 'escape' medication and when the patient has to stop the treatment because of side effects as a result of the treatment.

Missing values are only expected when a measurement could not be accomplished and/or forgotten so that no two successive measurements can be evaluated and the end point will not be determined with certainty. Everything has to be done to avoid this type of missingness. This type of missingness is estimated to be very small.

A second type of missing values can be created by patients who develop a surgical complication and are not related to the treatment (eg bleeding) resulting in its cessation.

This is estimated at less than 1%.

Given the occurrence of both types of missing values is estimated to be low and assumed to be unrelated to the outcome variable or treatment, a sensitivity analysis will be used in the research (best, worst and complete case scenario).

Previously, a success rate of 75% was reported for the use of PCA. With classical treatment, for example, in the literature on pain control, a target was achieved in 67% of patients. On this basis, a target of 65% is set as the absolute minimum.

The treatment will be evaluated as efficient when a 95% Wilson Score Confidence Interval for the success rate has a lower limit higher than 0.65.

For possible center effects, an ICC = 0.01 is assumed (values between 0 and 0.15 are realistic according to Vierron (2006), and in table 3 of Adams (2004) 0.01 is the median).

If it can be assumed that as many patients can be recruited in the two centers, 40 patients will be recruited in 2 centers with an ICC = 0.01, that the corrected sample size is only 57, or so this clustered patient group of 2 X 40 patients can only if 57 independent patients are seen (Killip 2004).

80/2 = 40

ESS = 40 * 2 / (1 + 0.01 * (40)) = 57

Recruiting sixty-eight patients in each center will lead to a corrected sample size of 80. The number of centers is the limiting factor here.

If the drop-out rate is estimated at 1%, then the sample size should be increased, so that the corrected sample size allows 1% drop-out to achieve the necessary sample size at the end of the study. Eg. 80 / 0.99 = 81.

7. Independent Ethics Committee and Competent Authority

The Zalviso trial received FAGG approval on 10-DEC-2019 and approval of the Ethical Committee on 29-JAN-2020.

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1.0 dd 11Mar2019* - *ICF version 2.0 dd 07Jan2020* - *Nurse handleiding pocket* - *Patient folder pre-op DU,FR* - *Patient folder post-op DU,FR* - *Label v 1.0 dd 12Nov2019* - *CRF v 1.0 05Nov2019* - *EOC nurse/physio/patient DU, FR v 1.0 22Oct2019* - *NRS score DU, FR v 1.0 12Nov2019* - *SmPC Zalviso dd 05Feb2019*	***Approval date Central EC:*** *29Jan2020*	***Approval date FAMPH:*** *10Dec2019*
Amendment 1: - *Prolongation trial dd 01Jul2021* *Prolongation trial with 2 months, end date 31Oct2021*	***Approval date Central EC:*** ***28Jul2021***	***Approval date FAMPH:*** *NA*

8. Results

8.1 Subject enrollment and demographics

Site	Not active yet?	Active?	Closed?	Number of Subjects included?	Date of first inclusion?	date of site closure (LPLV)
UZ Ghent	☐	☒	☐	20	26MAY2020	16MAR2023
Yperman ZH	☐	☒	☐	70	15JUN2020	19AUG2021

UZ Ghent

Age range	No of female subjects	No of male subjects	Total No of subjects
< 65 years	9	4	13
≥ 65 years	2	5	7

Yperman ZH

Age range	No of female subjects	No of male subjects	Total No of subjects
< 65 years	23	19	42
≥ 65 years	13	14	27

UZ Ghent

	Study Arm (if applicable)	Number of subjects completed	Number of subjects prematurely discontinued
Arm A	Zalviso® 15µg/tablet	20	0

Yperman ZH

	Study Arm (if applicable)	Number of subjects completed	Number of subjects prematurely discontinued
Arm A	Zalviso® 15µg/tablet	69	1

In the trial a maximum of 156 subjects were planned to be included. The accrual rate in UZ Ghent did not resemble the planned accrual rate due to other studies targeting the same population, patients preferring general anesthesia.

Furthermore there were issues with the availability of the materials/IMP as the pharmaceutical company Grünenthal decided to terminate the license supply agreement for Zalviso® in Oktober 2020. Therefore in UZGhent only 20 patients were included.

In Yperman ZH the accrual rate resembled the planned accrual rate : the last visit of the last patient was on 16-JUN-2021.

8.2 Study specific results

Study results are not available yet.

The data are available in the REDcap program and will be analyzed shortly.

9. Safety

There have been no Serious Adverse Events in UZ Ghent or Yperman ZH.

SAE Overview				
Subject ID	*Study Arm (if applicable)*	*SUSAR (Y/N)*	*SAE Description*	*Outcome (ongoing, resolved, death, ...)*

10. Device deficiencies

NA

11. Protocol deviations

UZ Ghent : all major protocol deviations were rescue medication related.

Patient 001 : refused 3 times to take rescue medication when NRS ≥4, and preferred to wait or take a Zalviso tablet.

Patient 005 : preferred to take a Zalviso tablet instead of rescue medication.

Patient 008 : was given resue medication, when he should have taken an extra Zalviso tablet.

Patient 009 : received rescue medication twice, when Zalviso should have been taken.

Patient 017 : asked twice for rescue medication, when he should have taken a Zalviso tablet

A flowchart on when to administer resue medication accompanied every patient ; the staff was reminded of the use of rescue medication with every trial participant.

Yperman ZH : no major protocol deviations were reported.

12. Discussion and overall conclusions

Our interventional study tested whether the Sublingual Sufentanil Tablet System (SSTS) is en efficient and safe analgesic technique allowing fast track rehabilitation after total knee arthroplasty. Efficiency was defined as more than 75% of the treated patients demonstrated NRS less than 4 during 48 hours postoperatively, in addition to basic pain treatment with paracetamol and NSAID. The research took place in two hospitals : Ghent University Hospital (coordinating hospital) and Yperman Hospital in Ieper.
The clinical experience with the new analgesic technique SSTS was very favorable in both hospitals. The included patients were comfortable and in most cases could ambulate on the

postoperative day 1. In the Yperman Hospital many patients were able to walk on the day of operation.
The majority of patients were satisfied and were discharged from the hospital within 3 days after surgery.
Nevertheless, there is no avalilable statistical analysis of data on primary (cumulative time of pain scores 48 hours postoperatively) or on secondary endpoints. The progress of the study was negatively impacted by the COVID pandemic as many of elective surgical procedures were postponed. This led to a long-term recruitment of patients and even a stoppage of recruitment in the Ghent hospital.

The inclusions of 70 patients in the Yperman hospital has ended. All data is available in the REDcap program and will be analyzed shortly.

The number of patients included in Ghent University Hospital is limited to 20 of 68 and therefore it is impossible to draw any conclusions at the moment.

Conclusions after clinical observations. The dosing system of SSTS Zalviso allows controlled administration of potent analgesics that allows the patient to autonomously control postoperative analgesia and, given the predictably rapid effect of sublingual sufentanil, also effectively anticipate painful procedures such as mobilization exercises after orthopedic surgery. Compared to traditional intravenous patient-controlled analgesia, patient mobility with this sublingual system is not restricted by intravenous lines. The system also requires less follow-up and technical control because it does not need to be programmed and provides medication for a continuous period of 48 to 72 hours. It thus combines the advantages of a PCA with those of maximum freedom of movement and less side effects.

13. References

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