26 April 2018
EMA/302958/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dzuveo

International non-proprietary name: sufentanil

Procedure No. EMEA/H/C/004335/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Al	Aluminium
APAP	Acetaminophen
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASMF	Active Substance Master File
AUC	Area under the curve
BHT	Butylhydroxytoluene
CAS	Chemical Abstracts Service
CE	Conformité Européene
CFU	Colony Forming Unit
Cmax	Maximum concentration
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CTD	Common Technical Document
CTM	Clinical Trial Material
DOE	Design of Experiments
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMA, EMEA	European Medicines Agency
EPCRS	European Pharmacopoeia Certified Reference Substance
EU	European Union
F	Female
FDA	Food and Drug Administration
FRC	functionality related characteristic
FT-IR	Fourrier transform infrared spectroscopy
GC	Gas Chromatography
GD	Gestation Day
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	healthcare professionals
HDPE	High Density Polyethylene
HED	Human Equivalent Dose
HPLC	High Performance Liquid Chromatography
HPMC	Hypromellose
HSDB	Hazardous Substances Database
i.v.	Intravenous
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP/OES	Inductively Coupled Plasma Optical Emission Spectroscopy
ID	identification
IDR	Intrinsic dissolution test
INN	International Non-proprietary Name
IPC	In-process control
IR	Infrared
IU	International Unit
KF	Karl Fischer titration
L.S.	Label Strength
LC	Liquid Chromatography
LD50	Lethal dose for 50% of animals
LDPE	Low Density Polyethylene
LOD	(1) Loss on Drying, (2) Limit of Detection

LOQ	(1) Limit of Quantification, (2) List of Question
M	Male
MA	Marketing authorization
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
N/A	Not Applicable
NLT	Not Less Than
NMR	Nuclear magnetic resonance
NMT	Not More Than
NOAEL	No Adverse Effect Level
NT	Not Tested
Patheon CRO	Patheon Pharmaceuticals Inc., Cincinnati Operations
Patheon TRO	Patheon Pharmaceuticals Inc., Toronto Operations
PCA	Patient controlled analgesia
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PP	Polypropylene
ppm	Parts Per Million
PVP	Polyvinylpyrrolidone
QTPP	Quality Target Product Profile
RFID	Radiofrequency Identification
RH	Relative Humidity
RP	Reversed Phase (chromatography)
RRT	Relative Retention Time
RS	Related substance
RSD	Relative Standard Deviation
RT	Room Temperature
SDA	Single Dose Applicator
SmPC	Summary of Product Characteristics
SST	Sufentanil Sublingual Tablet
TDI	Tolerable Daily Intake
TK	Toxicokinetic
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalitis
TTC	Threshold of Toxicological Concern
USAN	United States Adopted Name
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 2 March 2017 an application for Marketing authorisation to the European Medicines Agency (EMA) for Dzuveo, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2015. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Sufentanil 30 µg sublingual tablet is indicated for the management of acute moderate to severe pain in adult patients in a medically supervised setting (see section 4.2.).

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioavailability study with the reference medicinal product Sufenta Forte Solution for injection 0.05mg/ml and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Sufenta Forte solution for injection 0.05mg/ml
- Marketing authorisation holder: Janssen-Cilag B.V.
- Date of authorisation: 22-06-1982
- Marketing authorisation granted by:
  - Member State (EEA) : Netherlands
  - National procedure
- Marketing authorisation number: RVG 09233

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Sufenta Forte solution for injection 0.05mg/ml
- Marketing authorisation holder: Janssen-Cilag B.V.
- Date of authorisation: 22-06-1982
- Marketing authorisation granted by:
  - Member State (EEA) : Netherlands

- National procedure

- Marketing authorisation number: RVG 09233

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Sufenta Forte solution for injection 0.05mg/ml
- Marketing authorisation holder: Janssen-Cilag B.V.
- Date of authorisation: 22-06-1982
- Marketing authorisation granted by:
  - Member State (EEA) : Netherlands
  - National procedure
- Marketing authorisation number: RVG 09233
- Bioavailability study number: SAP101

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kolbeinn Gudmundsson Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 2 March 2017.
- The procedure started on 23 March 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 June 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 June 2017.

- During the meeting on 20 July 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2017.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
    - GCP inspections at two investigator sites and a CRO site located in the United States were performed between 7-25 August 2017. The outcome report of the inspection carried out was issued on 29 September 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2018.
- During the PRAC meeting on 8 February 2018, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 February 2018, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 March 2018.
- During the meeting on 26 April 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dzuveo on 26 April 2018.

2. Scientific discussion

2.1. Introduction

Problem statement

The Marketing Authorisation Application for Dzuveo, sufentanil sublingual tablet 30 µg, has been submitted for the management of moderate to severe acute pain in adult patients.

About the product

Dzuveo (sufentanil 30µg sublingual tablet, (also referred to as "SST 30 µg") is a non-invasive opioid analgesic administered by healthcare professional (HCP) via the sublingual route. Dzuveo 30 µg sublingual tablet is packaged in a single use, disposable, single-dose applicator (SDA). Because each sublingual tablet is very small, the SDA helps the HCP administer the tablet to the patients' sublingual space. Dosing is as required (prn), subject to a one hour minimum dosing interval.

Sufentanil is a synthetic, potent opioid with highly selective binding to µ-opioid receptors. Sufentanil binds to non-human primate µ-opioid receptors with14-times higher affinity than morphine.

Analgesia induced by sufentanil is thought to be mediated via activation of µ-opioid receptors primarily within the CNS to alter processes affecting both the perception of and emotional response to pain.

Alterations in the release of various neurotransmitters from afferent nerves sensitive to painful stimuli may be partially responsible for the analgesic effects.

Type of Application and aspects on development

This Application for a marketing authorisation of Dzuveo is submitted under Article 10(3) of Directive 2001/83/EC ("hybrid" Application) using Sufenta solution for injection as reference medicinal product. Sufenta has been authorised in the Netherlands since 1978 as an anaesthetic-analgesic. Sufenta contains the same active substance as Dzuveo but it is administered via the intravenous or epidural route.

The Application was supported by quality, non-clinical and clinical data. A dedicated clinical program was conducted to characterize the pharmacokinetics of sublingual sufentanil and establish efficacy and safety of this new route of administration in the new indication.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an immediate release sublingual tablet containing 30 µg sufentanil (as citrate salt) as active substance.

Other ingredients are: mannitol (E421), calcium hydrogen phosphate, hypromellose, croscarmellose sodium, indigo carmine (E132), stearic acid and magnesium stearate.

The product is available in polypropylene (PP) single-dose applicators, which are packaged in polyester film/LDPE/aluminium foil/LDPE sachets with an oxygen absorber as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of sufentanil citrate is *N*-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-*N*-phenylpropanamide citrate or *N*-[4-(methoxymethyl)-1-[2-(thiophen-2-yl) ethyl] piperidin-4-yl]-*N*-phenylpropanamide citrate corresponding to the molecular formula $C_{22}H_{30}N_2O_2S.C_6H_8O_7$. It has a relative molecular mass of 587.7 g/mol and the following structure (Figure 1):

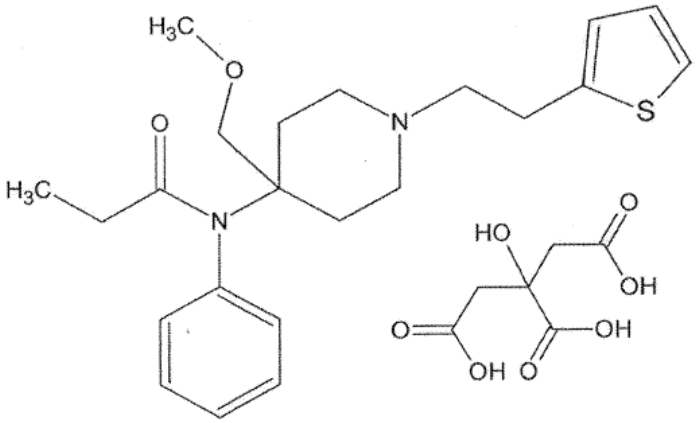


Figure 1: Sufentanil citrate structure

The structure of sufentanil citrate was confirmed by ^{1}H and ^{13}C NMR spectroscopy, FT-IR spectroscopy, and mass spectrometry.

The active substance is a white to off-white crystalline non-hygroscopic solid, soluble in water and sparingly soluble in ethanol and acetone. Two polymorphic forms of the active substance are known. XRPD patterns of 3 production scale batches from the proposed manufacturer indicated that the same polymorphic form is routinely produced. However, since sufentanil citrate is dissolved in ethanol as part of the finished product manufacture, the polymorphic form is not considered important. Whilst particle size is also not deemed important, the sufentanil citrate is sieved to ensure a consistent dissolution profile for secondary manufacture.

Sufentanil citrate is achiral.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Sufentanil citrate is synthesized by a single manufacturer in eight main steps using commercially available and well defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin, fate and purge and were characterised. The purge of genotoxic reagents and by-products has been demonstrated in intermediates made on commercial scale. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The active substance is packaged in type II amber glass bottles with phenolic resin closure which complies with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specifications used by the finished product manufacturer includes tests for appearance, identity (IR, UV, HPLC), identity of counter ion (USP), assay (HPLC, titration), related

substances (HPLC), loss on drying (Ph. Eur.), heavy metals (USP) and appearance of solution (Ph. Eur.). The tests and limits are consistent with the Ph. Eur. monograph.

Impurities present at higher than the qualification threshold according to ICH Q3A have been qualified by toxicological and clinical studies and appropriate specifications have been set. The applicant has demonstrated the purge of mutagenic materials used in the process.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standard of the active substance has been provided.

Batch analysis data on three production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 15 production scale batches of active substance from the proposed manufacturer stored in either the proposed commercial container, or for earlier batches, a container closure system representative of that intended for the market (a smaller scale version of the commercial pack) for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, loss on drying, assay (by titration and HPLC), related substances and degradation products. The analytical methods used were the same as for release, and were stability indicating. One batch gave out of specification results (too high) for assay at the 3, 6 and 36 month time points. This was linked to an overcharge of sufentanil base during the salt formation and the process was modified accordingly for the manufacture of subsequent batches. Health hazard evaluation and toxicology assessment determined the small amount of Sufentanil free base present in those batches of sufentanil citrate posed little or no health concern to patients. There were no other significant trends in any batches under any storage condition.

Forced degradation studies were carried out under conditions of heat (up to 150 ^{o}C), acid or base hydrolysis, and oxidation in solution. Degradation was observed on refluxing in acid or base, and in the presence of hydrogen peroxide. Exposure to oxygen is thus kept to a minimum.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container, tightly closed and stored in a well-ventilated area.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a blue-coloured flat-faced immediate release sublingual tablet with rounded edges containing sufentanil citrate equivalent to 30 µg sufentanil. It is 3 mm in diameter and 0.85 mm thick with a nominal tablet weight of 7.40 mg.

The finished drug product is defined as a single sufentanil sublingual 30 µg tablet packaged in a polypropylene single dose applicator (SDA) in a PE/Al laminate foil pouch together with a StabilOx oxygen absorber. A diagram of the applicator, containing the tablet, is shown in Figure 2:

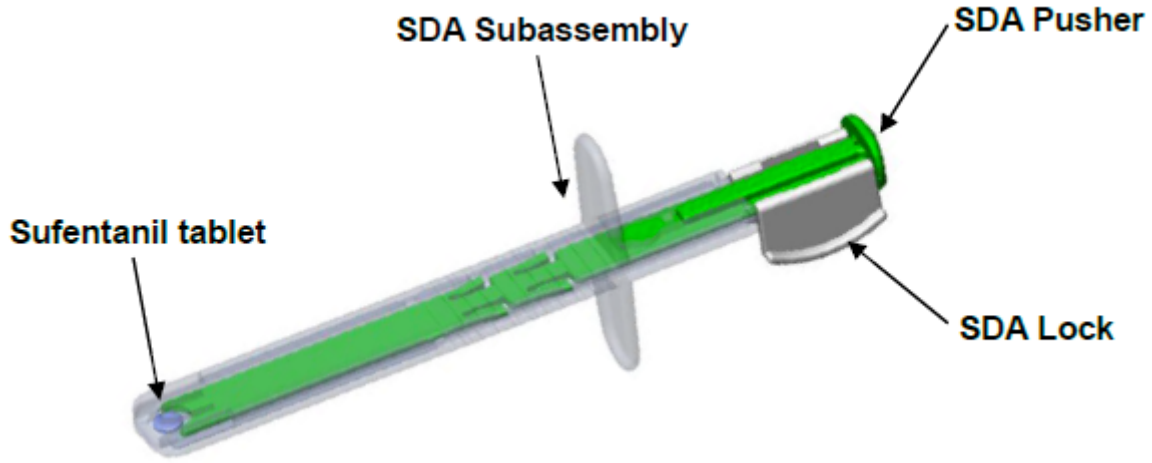


Figure 2: the single dose applicator for Dzuveo

The developed 30 µg formulation is essentially similar to a previously-developed 15 µg tablet used in another development program, with the exception of a doubling of active substance content and a change of colorant. The tablet size, shape, weight and manufacturing process are identical. Development work was conducted on the initial 15 µg sublingual tablet and then transferred to the 30 µg formulation. Several verification studies were conducted throughout the development of the 30 µg tablet to assure that these small changes did not affect the overall product performance.

Sufentanil is highly potent and thus constitutes only a minor proportion of the finished tablet composition (0.4%). In order to ensure content uniformity, it is dissolved in ethanol before spraying onto the excipients before granulation.

At the start of the project, a quality target product profile (QTPP) was defined. Sufentanil has high first-pass metabolism which rules out the oral route. The citrate salt is readily soluble in aqueous media, is rapidly absorbed via the oral mucosa, and the sublingual route is non-invasive. The aim was to develop a very small tablet with minimal taste to minimise saliva response and the possibility of swallowing the drug, and to minimise patient discomfort. The tablet needs to remain in the sublingual space for long enough to ensure complete drug release which should be fast enough to ensure the required response and ensure plasma levels reach targets within the therapeutic window. The tablets need to be robust enough to remain intact during usage and sufficiently stable to allow a reasonable shelf-life. Given the low dose, content uniformity is vital.

Excipients were chosen based on compatibility with the active substance and in order to adapt tablet properties to the above-mentioned requirements. Given the sublingual delivery method, mannitol was chosen as the major formulation component due to its sweet taste and aqueous solubility. Hypromellose is added in order to improve adhesion of tablets to the sublingual cavity. Croscarmellose was included as a disintegrant and the amount added was optimised in order to afford rapid tablet disintegration without compromising the bioadhesion characteristics. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Critical quality attributes (CQAs) were defined (assay, active substance and finished product purity and stability, content uniformity, active substance dissolution and device compatibility) and are appropriate for the chosen dosage form. Potential critical process parameters (CPPs) were identified for each process step by means of formalised risk assessment. Potential CPPs identified to have a medium or

high impact risk on finished product CQAs were investigated in more detail, applying statistical Design of Experiments, as well as univariate experiments. The relationship between CQAs and CPPs has been discussed in detail. Based on the results of the performed experiments, operating parameters and in-process controls (IPC) were established to assure manufacturing of a robust product in reproducible quality. The dissolution method was shown to be discriminatory against different levels of hypromellose which is the excipient with the largest impact on dissolution rate. Changes to other manufacturing parameters in the ranges studied did not impact the dissolution profile of the finished product.

An overage of sufentanil citrate is applied to compensate for an equivalent loss in assay during the manufacturing process, specifically, the granulation step. The loss of active substance has been investigated and only part of the lost material can be accounted for. This is considered acceptable as the assay method has been shown to pick up changes in active substance content.

Content uniformity was originally investigated on the blend prior to tableting. However, the low active substance content and overall low batch size made this inaccurate. Therefore, the applicant applies stratified testing of content uniformity in tablets prior to release to ensure that the active substance is evenly distributed.

The primary packaging is a PP single-dose applicator packaged inside a polyester film/LDPE/aluminium foil/LDPE sachet with an oxygen absorber. The packaging materials are inert and are commonly used for drug products and comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The device is fully integrated at the time of placing on the market (i.e. no assembly of the medicine part is needed before administration). Hence, no CE marking for the device is required.

Manufacture of the product and process controls

The manufacturing process consists of production of bulk tablets followed by insertion into the applicator. The process is considered to be a non-standard manufacturing process. The process for manufacturing the bulk tablets consists of 5 main steps: blending of intra-granular excipients; wet granulation using a solution of sufentanil dissolved in ethanol followed by drying; blending with extra-granular excipients followed by milling; compression to form tablets; bulk packaging.

Major steps of the manufacturing process have been validated on three consecutive production scale batches of finished product. Although this information was not provided with the initial submission, resulting in a major objection, the applicant was able to provide complete validation data during the procedure. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this type of manufacturing process and pharmaceutical form. In particular, tablets are checked for weight, thickness, resistance to crushing and friability following compression to ensure that the tablets are of consistent size and are sufficiently robust. In addition, visual inspections are carried out during packaging to ensure that each applicator contains a single tablet and that it has been correctly assembled.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (HPLC, 2 separate methods), assay (HPLC), content uniformity (Ph.

Eur.), related substances (HPLC), dissolution (Ph. Eur.), water content (KF) and microbiological purity (Ph. Eur.). A further test to check adequate dispensing of tablets from the applicator is carried out.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. A risk assessment for the presence of elemental impurities was carried out in accordance with ICH Q3D. The conclusion was that given the small size of tablets, the nature of raw materials, and the manufacturing equipment, the likelihood of elemental impurities being present above the PDE is extremely low.

Batch analysis results are provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches were manufactured by the proposed commercial manufacturer using active substance from the ASMF holder and packaged in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, dissolution, impurities, water content and microbiological quality. The analytical procedures used have been shown to be stability indicating. No significant changes to any of the measured parameters were observed.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples exposed in the open, or in the applicator showed an increase in impurities and a corresponding drop in assay. However, tablets stored in the applicator inside the commercial foil pouch were found to be stable. The product should therefore be kept inside the foil pouch in which it is supplied. Samples were also tested following exposure to different temperature conditions (-20, 5 or 50 ^{o}C) and were found to be stable.

Stability studies were also carried out on in-process intermediates in order to assign suitable hold times. Samples of both granulated blend and bulk tablets were stored in their respective packages, inside foil pouches containing oxygen absorbers. The samples were found to be stable and thus, the proposed maximum holding times of 6 months for the granulated blend and 7 months for the bulk tablets are deemed acceptable.

Based on available stability data, the proposed shelf-life of 36 months in the store in the original package in order to protect from light and oxygen as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. A sublingual tablet was

developed in order to by-pass first pass metabolism. The chosen citrate salt is readily dissolved and rapidly absorbed *via* the oral mucosa, giving a rapid onset of action. The sublingual tablets are packaged in a single-dose applicator, which is an integral part of the product and does not need a CE mark.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

The reference product Sufenta is approved for IV and epidural administration, therefore substantial elements of the nonclinical profile have already been established. The systemic pharmacological, pharmacokinetic and toxicological properties of sufentanil have already been demonstrated. To support the application for the oral sublingual route, targeted pharmacokinetic studies have been performed in dogs by comparative assessment of absorption after IV, oral, buccal and sublingual single dose administration. The toxicological program included GLP compliant repeat-dose toxicology and local tolerance studies in Golden Syrian hamster after buccal administration.

These bridging data has been previously assessed by the CHMP in the evaluation of Marketing Authorisation Application for Zalviso (sublingual sufentanil 15 mg).

2.3.2. Pharmacology

No separate studies have been performed by the Applicant.

2.3.3. Pharmacokinetics

A limited nonclinical pharmacokinetic program was conducted to demonstrate the feasibility of the sublingual route of administration. Absorption studies were conducted in Beagle dogs using two experimental formulations of sufentanil. The sublingual route of exposure was compared to the intravenous, oral and buccal routes of administration.

Absorption

In two absorption studies in dogs the sublingual formulation systemic bioavailability was between 57%-and 60%. The formulation containing protonated sufentanil molecules (citrate salt) showed faster absorption, but bioavailability was significantly lower, which might be due to different absorption pathways. Another factor which is important regarding kinetics is the site where tablet was disposed to. It did not influence the extent of absorption but after buccal administration the Cmax was less than half of the sublingual way. As expected, sufentanil had poor oral bioavailability (less than 10%).

Although the PK studies did not use the proposed clinical formulation, they provide supporting data to justify the use of sublingual sufentanil for the suggested therapeutic indication.

Distribution, Metabolism, Excretion

No separate studies were conducted but relevant data were summarised by the Applicant based on published literature.

2.3.4. Toxicology

No single dose toxicity studies, genetic toxicology studies, carcinogenicity studies or reproductive toxicity studies were conducted by the applicant. Instead, references were made to published literature and data available for the reference product, Sufenta.

A limited toxicology program was conducted to evaluate the local and systemic effects of sufentanil in sublingual tablet using buccal administration to hamsters. These bridging studies were designed to determine if the new route of exposure resulted in different adverse effects versus what is observed with the approved routes of administration.

Repeat dose toxicity

SST was evaluated in repeat dose studies in hamsters for 7 days (WIL-591012) and 28 days (WIL-591014). The results of the 2 studies were very similar. Clinical signs typical of opioid pharmacology (rigid body, hypoactivity, respiratory depression) were observed at all doses. The severity of the effects increased with dose. Dose dependent decreases in body weight were observed in both studies. Increased red blood cell (RBC) count, haemoglobin and hematocrit were observed, suggestive of hemoconcentration due to dehydration. There were no significant local effects nor were there any effects on clinical chemistry, organ weight, gross necropsy or histopathology. All effects were reversible during the recovery period. It was concluded that the pharmacological and toxicological effects of SST were typical of what would be expected from an opioid agonist.

Based on study WIL-591014, hamsters tolerated SST at sufentanil doses up to 180 µg/day (No Observed Adverse Effect Level (NOAEL)) via buccal administration. The adverse effects identified in this study are consistent with exaggerated pharmacological action of an opioid agonist. At the Maximum Tolerated Dose (180 µg/day), no additional target organs were identified. This dose is equivalent to a sufentanil dose of about 13,000 µg/day in the clinic.

Local tolerance

To evaluate the local tolerance of SST, hamsters were subcutaneously administered naltrexone, an opioid antagonist, prior to SST administration. A dose range finding study (Study 692063) established that a 10 mg/kg naltrexone dose was adequate to block the opioid effects of 400 µg/day sufentanil (SST 80 µg, 5 times/day). In the pivotal study (Study 692032), hamsters tolerated 400 µg/day sufentanil (SST 80 µg, 5 times/day, 2 hours apart) for 4 days with minimal effects on the gross pathology and histopathology of the cheek pouch. It was concluded that SST has minimal potential for local irritation.

2.3.5. Ecotoxicity / environmental risk assessment

Phase I assessment demonstrates that sufentanil citrate is not likely to achieve sufficient penetration into the surface water (the expected primary compartment) to trigger a Phase II assessment. It is therefore concluded that a Phase II environmental assessment of sufentanil citrate is not required.

Table 1. Summary of main study results

Substance (INN): Sufentanil			
CAS-number (if available):			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107	3.24	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.24	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0036	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

Sufentanil is a well-known synthetic mu opioid receptor agonist analgesic. Non-clinical pharmacology, pharmacokinetics and toxicology including the primary effect on analgesia and all other opioid actions are well-known. Since the Application is based on Article 10(3) of Directive 83/2001/EC, the applicant submitted mainly bibliographic data.

The Applicant conducted three *in-vivo* studies in male beagle dogs. Absorption into the systemic circulation and substantial systemic bioavailability of 58 and 75% after sublingual administration, due to avoidance of intestinal and first-pass liver metabolism, was showed. Oral bioavailability was shown to be poor indicating less concern in case of accidental swallowing of the drug.

The applicant identified four impurities and it was concluded that none of them are genotoxic.

The applicant also summarized published literature concerning single dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, which in general is sufficient to conclude on safety of the product candidate.

2.3.7. Conclusion on non-clinical aspects

Taken together, the submitted non-clinical data supports the clinical use of Dzuveo in the proposed dose and indication.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program for SST 30 µg included 1 Phase 2 study (SAP202), and 3 Phase 3 studies (SAP301, SAP302, and SAP303). Two of these were randomized, double-blind, placebo-controlled clinical trials (Study SAP301 and Study SAP202) conducted in 221 patients (SST 30 µg, N = 147; placebo, N = 74) using well-recognized postoperative pain models (elective abdominal surgery and elective bunionectomy). Efficacy of SST 30 µg was additionally supported by results from 2 Phase 3, open-label studies (SAP302, and SAP303, N = 216).

Studies previously submitted and evaluated for Zalviso MAA were also taken into account.

Table 2. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
BA	IAP102	5.3.1.1	Single-dose PK of different routes of administration	Single-center, open-label, randomized, 6-sequence, 4-treatment, 4-period, crossover	SST 15 mcg; single dose; sublingual SST 15 mcg; single dose; buccal SST 15 mcg; single dose; oral Sufentanil 15 mcg over 1 minute; single dose; IV All subjects received naltrexone 50 mg	25 enrolled; 22 completed	Healthy subjects	Single dose	Completed; Full
PK	SAP101	5.3.3.1	Single- and multiple-dose PK comparing SST 30 mcg with SST 15 mcg	Single-center, randomized, open-label, 2-sequence, 4-treatment, 4-period, crossover study in naltrexone-blocked subjects	30 mcg IV; 2 x SST 15 mcg dosed 20 minutes apart; SST 30 mcg, single dose SST 30 mcg, 12 consecutive doses every hour	40 enrolled; 34 completed	Healthy subjects	Up to 12 hours	Completed; Full
PK	ARX-F01-01	5.3.3.1	Single- and repeat-dose PK of different doses	Single-center, open-label, 4-part, sequential	**Part 1** Sufentanil 5 mcg over 10 minutes; single dose; IV SST 2.5, 5, and 10 mcg; single dose; sublingual **Part 2** SST 5 mcg; Q 10 minutes for 4 doses; sublingual **Part 3** Day 0 Sufentanil liquid 5 mcg; single dose; sublingual OR Sufentanil 5 mcg over 10 minutes; single dose; IV Day 1 SST 10 mcg; single dose; sublingual Day 2 SST 10 mcg; Q 20 minutes for 4 doses; sublingual **Part 4** Day 4 Sufentanil 50 mcg over 20 minutes; single dose; IV Day 7 SST 80 mcg; single dose; sublingual All subjects received naltrexone 50 mg	22 enrolled; 22 completed	Healthy subjects	**Part 1** 4 single doses with 1-day washout **Part 2** 4 doses **Part 3** Day 0 Single dose Day 1 Single dose Day 2 4 doses **Part 4** Day 4 Single dose Day 7 Single dose	Complete; Abbreviated

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
PK	IAP101	5.3.3.1	Single and repeat-dose PK	Single-center, open-label, 2-treatment, 2-period, fixed-sequence, crossover	SST 15 mcg; single dose; sublingual SST 15 mcg; Q 20 minutes for 40 doses; sublingual All subjects received naltrexone 50 mg	40 enrolled; 38 completed	Healthy subjects	Single and repeat dose (40 doses over 13.3 hours) separated by 48-hour washout	Complete; Full
PK	IAP104	5.3.3.4	PK drug interaction (ketoconazole)	Single-center, open-label, 2-treatment, 2-period, fixed-sequence	SST 15 mcg; single dose; sublingual SST 15 mcg; single dose; sublingual + ketoconazole tablet 400 mg; Q 1 day for 3 doses; oral All subjects received naltrexone 50 mg	19 enrolled; 18 completed	Healthy subjects	Single dose with or without keta-conazole	Completed; Full
PK	ACX-PPK-259-001	5.3.3.5	Population PK analysis for the aggregate ARX-01 and ARX-04 database	various[a]	SST 30 mcg; single and multiple-dose	1066 subjects from 11 studies	Healthy and postoperative patients	various[a]	Completed; Full
Safety/ Efficacy	SAP202	5.3.5.1	Efficacy and safety	Multicenter, randomized, double-blind, placebo control	SST 30 mcg; PRN; sublingual SST 20 mcg; PRN; sublingual Placebo; PRN; sublingual	101 enrolled; SST 30 mcg: treated 40; completed 35 SST 20 mcg: treated 40; completed 37	Postsurgical adult patients following bunionectomy alone or with hammertoe repair	Up to 12 hours	Completed; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
						Placebo: treated 20; completed 19			
Safety/ Efficacy	SAP301	5.3.5.1	Efficacy and safety	Multicenter, randomized, double-blind, placebo control	SST 30 mcg; PRN; sublingual Placebo; PRN; sublingual	161 enrolled and dosed enrolled; SST 30 mcg: treated 107; completed by 24-hours 102 Placebo: treated 54; completed by 24-hour 41	Postsurgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery	Up to 48 hours	Completed; Full
Safety[b]	IAP310	5.3.5.1	Efficacy andsafety	Multicenter, randomized, double-blind; placebo control	SST 15 mcg; PRN; sublingual Placebo	178 enrolled; SST 15 mcg: treated 114; completed by 48-hour 78 Placebo: treated 58; completed by 48-hour 27 78 included in ARX-04 ISS; SST 15 mcg: treated 51; Placebo: treated 27	Postsurgical adult patients following open abdominal surgery	Up to 72 hours	Completed; Full
Safety[b]	IAP311	5.3.5.1	Efficacy and safety	Multicenter, randomized,	SST 15 mcg; PRN;	426 enrolled; SST 15 mcg:	Postsurgical adult patients	Up to 72 hours	Completed; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
				double-blind; placebo control	sublingual Placebo	treated 315; completed 215 Placebo: treated 104; completed 43 196 included in ARX-04 ISS; SST 15 mcg: treated 142; Placebo: treated 54	following knee or hip replacement stratified by type of surgery (knee or hip)		
Safety[b]	ARX-C-001	5.3.5.1	Efficacy and safety	Multicenter, randomized, double-blind; placebo control	SST 5 mcg; PRN; sublingual SST 10 mcg; PRN; sublingual SST 15 mcg; PRN; sublingual Placebo	101 enrolled; SST 5 mcg: treated 24; completed 11 SST 10 mcg: treated 26 completed 9 SST 15 mcg: treated 20; completed 13 Placebo: treated 24; completed 7 27 included in ARX-04 ISS; SST 15 mcg: treated 12;	Postsurgical adult patients following knee replacement stratified within each site by 2 age groups: 45 – 60 years, and 61 – 80 years	Up to 12 hours	Completed; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
						Placebo: treated 15			
Safety[b]	ARX-C-005	5.3.5.1	Efficacy and safety	Multicenter, randomized, double-blind; placebo control	SST 10 mcg; PRN; sublingual SST15 mcg; PRN; sublingual Placebo	94 enrolled; SST 10 mcg: treated 29; completed 22 SST 15 mcg: treated 29; completed 25 Placebo: treated 30; completed 9 14 included in ARX-04 ISS; SST 15 mcg: treated 6; Placebo: treated 8	Postsurgical adult patients following open abdominal surgery stratified within each site by 2 age groups: 18 – 60 years, and 61 – 80 years	Up to 12 hours	Completed; Full
Safety/ Efficacy	SAP302	5.3.5.2	Efficacy and safety	Multicenter, open-label; no control	SST 30 mcg; PRN; sublingual	76 enrolled; SST 30 mcg: treated 76; completed 36	Emergency room setting – adult patients with pain due to trauma or injury	Up to 5 hours	Completed; Full
Safety/ Efficacy	SAP303	5.3.5.2	Efficacy and safety in older population	Multicenter, open-label in subjects over 40 years; no control	SST 30 mcg; PRN; sublingual	140 enrolled; SST 30 mcg: treated 140; completed 132	Post-surgical patients 40 years or older following any type of surgery	Up to 12 hours	Completed; Full
Safety[b]	IAP309	5.3.5.2	Efficacy and safety	Multicenter, randomized,	SST 15 mcg; PRN; sublingual	359 enrolled; SST 15 mcg:	Postsurgical adult patients	Up to 72 hours	Completed; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Patient Type	Duration of Treatment with Sufentanil	Study Status; Type of Report
				open-label, parallel-group; active control	Morphine 1 mg over 6 minutes; PRN; IV	treated 177; completed 146 Morphine: treated 180; completed 136 94 SST 15 mcg included in ARX-04 ISS	following open abdominal surgery or knee or hip replacement stratified by age (< 65 years and ≥ 65 years) and type of surgery (knee and other surgeries)		
Safety[b]	IAP309 Addendum	5.3.5.2	Efficacy and safety of ≤ 30 mcg/ hour of sufentanil vs. morphine	Post hoc analysis of IAP309	SST 15 mcg (≤ 30 mcg/ hour of sufentanil); PRN; sublingual Morphine 1 mg over 6 minutes; PRN; IV	SST 15 mcg: 42 received ≤ 30 mcg/ hour of sufentanil Morphine: treated 180; completed 136	Postsurgical adult patients following open abdominal surgery or knee or hip replacement stratified by age (< 65 years and ≥ 65 years) and type of surgery (knee and other surgeries)	Up to 72 hours	Completed post hoc analysis; Addendum
Safety[b]	ARX-C-004	5.3.5.2	Efficacy, safety, and PCA system functionality	Multicenter, open-label; no control	SST 15 mcg; PRN; sublingual	30 enrolled; SST 15 mcg: treated 30; completed 26 18 SST 15 mcg included in ARX-04 ISS	Postsurgical adult patients following knee replacement	Up to 12 hours	Completed; Full

Abbreviations: BA = bioavailability; BE = bioequivalent; IV = intravenous; N/A = not applicable; PCA = patient-controlled analgesia; PK = pharmacokinetic; PRN = pro re nata; SST = sufentanil sublingual tablet.
[a]Study ACX-PPK-259-001 was a population PK analysis that included data from subjects in the following studies in the ARX-04 (SST 30 mcg) program: SAP101, SAP202, SAP301, SAP303; and in the ARX-01 (SST 15 mcg) program: ARX-C-001, IAP101, IAP102, IAP104, IAP309, IAP310, IAP311.
[b]This study was conducted using a lower-dose SST (SST 15 mcg) and supports the safety of SST 30 mcg. One SST 30 mcg tablet was shown to be BE to 2 SST 15 mcg tablets dosed within 20 minutes of each other (SAP101). Those patients who took the second study dose within 20 to 25 minutes after the first study dose were included in the ARX-04 integrated summary of safety (ISS).

2.4.1. Pharmacokinetics

The applicant has submitted 1 BA and 5 PK studies to support the application for 30 µg sufentanil sublingual tablet. This MAA contained 1 new additional study, SAP101 but was partly relying on the clinical studies conducted for Zalviso (SST 15 µg): the BA study IAP102, the two PK studies IAP101 and ARX-F01-01 and the PK drug interactions study (ketoconazole) IAP104.

The results of the BA and PK studies submitted to support the marketing authorisation for SST 30 mcg showed that systemic exposure of sufentanil after Sufenta IV 30 mcg was greater than after single-dose SST 30 mcg. The mean bioavailability (F) approximately the same after administration of single-dose SST 30 mcg and 2 doses of SST 15 mcg, 53% and 59%, respectively. Median $CST_{1/2}$ was 2.33 hours after administration of either single-dose SST 30 mcg or 2 consecutive doses of SST 15 mcg compared to 0.10 hours following Sufenta IV 30 mcg.

The PK study SAP101 evaluated the single-dose and multiple-dose PK of sublingual administration of the SST 30 mcg formulation and compared the PK of the single dose to 2 doses of Zalviso (SST 15 mcg) administered 20 minutes apart. Additional PK modelling demonstrated that bioequivalence is maintained if the inter-dosing interval for the 15 mcg SST tablets is extended to 25 minutes which supports the applicability of safety data from clinical trials of ARX-01 (Zalviso 15 mcg) for use in this marketing authorisation application for the ARX-04 (SST 30 mcg). The applicant also submitted an

updated population PK analysis study ACX-PPK-259-001, which included concentration data from the Phase 1, 2 and 3 trials with the new SST 30 µg tablets additionally to that already obtained following SST 15 µg (Zalviso).

There were no relevant differences between any PK parameter ($AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$) after administration of single-dose SST 30 mcg when compared to that of 2 consecutive doses of SST 15 mcg (with 20 minutes between doses). For single-dose SST 30 mcg and 2 doses of SST 15 mcg (with 20 minutes between doses) the primary pharmacokinetic parameters $AUC_{0\text{-}inf}$ and C_{max} both had 90% CIs of the GMR that fell within the 0.8 to 1.25 range, supporting bioequivalence.

Sufentanil concentrations accumulated upon multiple dosing and steady stated was reached after 7 doses (or 360 minutes) of SST 30 mcg. After the last of 12 consecutive doses of SST 30 mcg, $AUC_{0\text{-}60}$ and C_{max} increased by 3.7 fold and 2.3 fold, respectively, compared to after the first dose. Median T_{max} was 8.92 hours after administration of multiple-dose SST 30 mg compared to 1.00 hour after administration of single dose SST 30 mcg. Median $CST_{1/2}$ was 2.33 hours regardless of whether observed after a single-dose or multiple-dose SST 30 mcg, demonstrating that there is a predictable and consistent offset after multiple dosing with SST 30 mcg. Geometric mean $AUC_{0\text{-}60}$ of the last dose for multiple-dose SST 30 (113.30 h*pg/mL) was greater compared to single-dose SST 30 mcg (30.27 h*pg/mL) and lower compared to $AUC_{0\text{-}720}$ for single-dose SST 30 mcg (186.79 h*pg/mL).

2.4.2. Pharmacodynamics

Since sufentanil has been used in clinical practice for decades and the legal basis of the application is Article 10(3) of Directive 2001/83/EC (hybrid application) no new PD clinical studies are required and none were provided.

No studies of healthy subject or patient pharmacodynamics were conducted. Pain is a subjective disease state and the dose and plasma concentration required for pain relief is highly variable. The sufentanil sublingual tablet 30 mcg will be administered by a Healthcare Provider to the patient on a “as needed basis (ie prn)” but no more frequently than every 60 minutes. Given the prn dosing regimen, and the relatively wide variability of patient interdosing intervals, it was not relevant to conduct a traditional PK/PD study as would be done with a fixed-dosing regimen product.

Sufentanil as a strong and efficacious µ opioid receptor agonist possesses all the well-known opioid effects such as analgesia, respiratory depression, euphoria, miosis, nausea, sedation, constipation, etc. This information is well-known the Applicant has not focused on discussing the details. Opioids in general has almost no off-target effects. The affinities for non-opioid receptors, enzymes (including CYP monooxigenases) or transporters are limited or negligible. Therefore, the lack of information about secondary pharmacodynamics of sufentanil is acceptable. Sufentanil can interact with other CNS depressants. It may augment the CNS depressant effects of barbiturates, tranquilizers, opioids, general anesthetics, or other CNS depressants (e.g., alcohol).

2.4.3. Discussion on clinical pharmacology

Bioequivalence was shown between single-dose SST 30 mcg and 2 consecutive doses of SST 15 mcg (with 20 minutes between doses). To validate inclusion of patients in the safety database who re-dosed SST 15 mcg up to 25 minutes (ie, all 323 patients requested for inclusion from the Zalviso program)

after the first dose, PK modelling was conducted to demonstrate the effect on drug concentrations when the second dose is administered 25 minutes after the first. Based on the absorption profile of sufentanil from the sublingual space, a 5-minute difference in timing of re-dosing a second SST (i.e., from the demonstrated bioequivalence of 2 x 15 mcg dosed 20 minutes apart to increasing this interval to 25 minutes) has negligible impact on the resulting sufentanil PK. Thus, this additional PK modelling has demonstrated that the bioequivalence found between SST 30 mcg and two SST 15 mcg tablets dosed within 20 minutes of each other is maintained if the inter-dosing interval for the 15 mcg SST tablets is extended to 25 minutes. Given the above analysis, and since the majority of the patients who dosed the second 15 mcg dose between 20 and 25 minutes also dosed a third SST 15 mcg within the first hour of dosing, and thus received a 50% higher dose exposure than ARX-04 (SST 30 mcg), inclusion of these patients is justified. The additional clinical studies performed using ARX-04 (30 mcg) provide a total safety database of 686 patients for ARX-04 (363 unique ARX-04 patients and 323 Zalviso patients).

The POP-PK model was validated, and the results are reported according to standards. The POP-PK of sufentanil sublingual tablets were described by the same two-compartment model with first-order oral absorption and a lag time as previously. In overall it seems that individual characteristics have moderate effects on the PK. Furthermore, the on-demand dosing makes the effect of the extrinsic and intrinsic factors on the PK parameters even less relevant. Further statistical analysis showed that baseline pain intensity is the only factor which controls the dose rate.

To understand the relationship between the maximum dose and the actual drug use, the Applicant was asked to compare the plasma sufentanil plasma levels following 15 and 30 µg SST tablets. The analysis showed that in the clinical trials with 15µg SST tablets the sufentanil plasma levels were higher. This higher sufentanil exposure for the SST 15 µg product can be explained by three key factors:

1)- The total possible hourly dosing with the SST 15 µg product is higher
2)- The SST 30 µg product is not self-administered
3) - The SST 15 µg studies only evaluated patients after major surgery in more severe conditions compared to patients in the studies with SST 30 µg tablets, and the Applicant showed total dose depends only on the intensity of the postoperative pain. Patients with the highest pain score (7 or more) demand one tablet more in average compared to the patients at the other end of spectrum (the pain score is 1 or less).

Dosage recommendation for elderly people was another concern. It is generally held that the pain threshold is generally higher in elderly. Therefore, it is not expected that the exposure will be higher due to the increased demand. POP-PK analysis revealed that the clearance decreases with age. However, older patients in the clinical studies were heavier and the clearance increases with the body weight, therefore the summary net of age is expected to be neutral. The Applicant sub-group analysis confirmed this expectation.

2.4.4. Conclusions on clinical pharmacology

The CHMP considered that the available clinical pharmacology data were suitable to support the Application for a marketing authorisation of Dzuveo. The product information adequately reflects relevant pharmacology data.

2.5. Clinical efficacy

2.5.1. Main clinical studies

The main support for efficacy of Dzuveo was provided by two placebo controlled trials. Due to design similarities between them, they are described side by side below.

SAP301

A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil Sublingual Tablet 30 mcg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery

SAP202

A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® for the Management of Acute Pain Following Bunionectomy Alone or with Hammertoe Repair

- **Study participants and treatments**

SAP301
This was a multicentre, randomized double-blind, placebo-controlled trial in adult patients who had undergone an ambulatory abdominal surgery normally performed as an outpatient procedure: abdominoplasty; open-tension-free inguinal hernioplasty (Lichtenstein repair with mesh); or laparoscopic abdominal surgery.

Following surgery, patients were assessed for pain intensity, vital signs, and oxygen saturation. Patients who continued to meet the entry criteria were randomly assigned in a 2:1 ratio to treatment with sufentanil 30 mcg or placebo, stratified by sex at each study site. Before study drug could be administered, the patient must have reported a pain intensity (PI) of ≥ 4 just prior to the first dose of study drug (baseline PI). The time of the first dose of study drug was the start of the 48-hour study period. A qualified healthcare professional (HCP) administered study drug to the patient's sublingual space using a single-dose applicator (SDA). Additional doses were administered by an HCP when requested by the patient over the next 48 hours, with a minimum re-doing interval of 60 minutes.

SAP202:
The study was a multicentre, randomized, double-blind, placebo-controlled trial for 12 hours in patients 18 to 80 years of age who were undergoing bunionectomy alone or with hammertoe repair.

Patients who met all inclusion and exclusion criteria following surgery were randomly assigned at a 2:2:1 ratio to treatment with sufentanil NanoTab 20 mcg, sufentanil NanoTab 30 mcg, or placebo NanoTab. Randomization was stratified within each site by 2 age groups: 18 to 64 years and 65 to 80 years.

Main inclusion and exclusion criteria at screening:
Inclusion Criteria at Screening

- Male or female patients who were 18 years of age or older.
- Study SAP202: Patients who were scheduled for a primary, unilateral, first metatarsal bunionectomy alone or with ipsilateral hammertoe repair with IV sedation and Mayo block local analgesia.
- Study SAP301: Patients who were scheduled to undergo one of the following procedures under general or spinal anesthesia that did not include intrathecal opioids during theoperation: abdominoplasty, open tension-free inguinal hernioplasty (Lichtenstein repair with mesh), or laparoscopic abdominal surgery.
- Study SAP301: Patients who were expected to have moderate-to-severe post-operative pain for at least 24 hours.
- Patients classified as American Society of Anesthesiologists class I to III.

Exclusion Criteria at Screening

1. Patients who had taken an opioid for more than 30 consecutive days, at a daily dose of more than 15 mg of morphine (or equivalent), within the past 3 months prior to surgery (e.g. more than 3 doses per day of Vicodin, Norco®, Lortab® with 5 mg hydrocodone per tablet).

2. Patients with a positive drug of abuse screen unless the positive test result was consistent with a prescribed medication.

3. Patients with a history of opioid dependence within 2 years before the start of the study, defined as meeting the DSM-IV-TR™Criteria for Substance Dependence (as specified in Appendix II of the study protocol [Appendix 16.1.1]).

4. Patients who had used any illicit drugs of abuse within 5 years before the start of the study.

5. Patients who had abused any prescription medication or alcohol within 1 year before the start of the study.

7. Patients who were currently taking monoamine oxidase inhibitors (MAOIs) or had taken MAOIs within 14 days of the first dose of study drug.

8. Patients with current sleep apnea that had been documented by a sleep laboratory study or were on home continuous positive airway pressure.

- **Objectives**

<u>SAP301:</u>

The primary objective of this study was to compare the efficacy and safety of the sufentanil sublingual tablet 30 mcg to the placebo sublingual tablet.

Secondary objectives were to assess patient ratings of pain intensity (PI) and pain relief (PR), time to perceptible and meaningful pain relief, percentage of patients requiring rescue due to inadequate analgesia, global assessments, and the use of rescue medication.

SAP202:

The primary objective of the study was to demonstrate the repeat-dose efficacy of sufentanil NanoTab 20 mcg and 30 mcg compared to placebo as determined by the time-weighted summed pain intensity difference (SPID) over the 12- hour study period (SPID12).

Secondary objectives were to demonstrate the efficacy of sufentanil NanoTab 20 mcg and 30 mcg over the first hour (single-dose efficacy; SPID1), patient ratings of pain relief (PR), time to perceived analgesia, time to meaningful analgesia, percentage of patients requiring rescue analgesics due to inadequate analgesia, and patient global assessment (PGA) of effectiveness and tolerability. An additional secondary objective was to evaluate the safety and tolerability of sufentanil NanoTab 20 µg and 30 µg.

- **Outcomes / endpoints**

The primary efficacy endpoint for both studies was the time-weighted SPID12 evaluated from the patient questionnaire data. Pain intensity was measured using an 11-point NRS with 0 (no pain) and 10 (worst possible pain).

The pain intensity difference (PID) at each evaluation time point after the initiation of the first dose is the difference in pain intensity at the specific evaluation time point and baseline pain intensity [PID (evaluation time after the first dose) = PI(baseline) – PI(evaluation time after the first dose)]. The time-weighted SPID12 is the time-weighted summed PID over the 12-hour study period.

Time-weighted SPID12 = Σ [T(i) – T(i-1)] x PID(i),

Where: T(0) = Time 0 (baseline), T(i) is the scheduled or unscheduled assessment time, and PID(i) is the PID score at time i for i=0 to 12 hours.

Study #	Primary Endpoint (ITT Population)	Key Secondary Efficacy Endpoints (ITT Population)
Placebo-controlled Phase 2 and 3 studies		
SAP301	Time-weighted SPID12; Pain intensity was measured on an 11-point NRS; data were pooled from all study centers and summarized for the ITT; missing data were imputed	1. SPID1 2. SPID24 and SPID48 3. TOTPAR12, TOTPAR24 and TOTPAR48 4. SPRID12, SPRID24, and SPRID48 5. Proportion of patients who terminate from the study due to inadequate analgesia 6. Proportion of patients requiring rescue medication due to inadequate analgesia 7. Proportion of patients and healthcare professionals who responded to the global assessments as "excellent" or "good" 8. Proportion of patients and healthcare professionals who responded in each category of the global assessments 9. PI at each evaluation time point 10. PID at each evaluation time point 11. PR at each evaluation time point 12. PRID at each evaluation time point; the PRID is the sum of PR and PID 13. Proportion of patients who complete 24 hours in the study and do not require study medication after the 24-hour study period 14. Time to first use of rescue medication 15. Total number of doses of study drug and rescue medication used over 48-hour study period 16. Mean duration of inter-dosing interval over the 48-hour study period 17. Time to onset of perceptible and meaningful pain relief
SAP202	Time-weighted SPID12 Pain intensity was measured on an 11-point NRS; data were pooled from all study centers and summarized for the ITT; missing data were imputed	1. Modified time-weighted SPID12 (with serial imputation for each use of rescue analgesics) over the 12-hour study period 2. SPID12 3. SPID1 4. PI at each time point 5. PID at each time point 6. PR at each evaluation time point 7. PRID at each evaluation time point; the PRID is the sum of PR and PID 8. TOTPAR12 9. Modified TOTPAR (with serial imputation for each use of rescue analgesics) over the 12-hour study period 10. Proportion of patients requiring rescue analgesics due to inadequate analgesia over the 12-hour study period 11. Proportion of patients who responded in each category of the Patient Global Assessment 12. Total number of doses used over the 12 hour study period 13. Time to first use of rescue analgesics and total number of doses of rescue analgesic used 14. Time to onset of perceived and meaningful analgesia

- **Sample size**

SAP301:

A sample size of approximately 180 patients (120 patients in the sufentanil 30 mcg treatment group and 60 patients in the placebo treatment group) was planned for this study assuming a 10% non-evaluable rate to ensure at least 159 patients (106 sufentanil-treated patients and 53 placebo patients) received study drug and had available primary efficacy data for analysis.
A sample size of 159 patients (106 sufentanil-treated patients and 53 placebo patients) was based on an effect size of 0.55 for the primary efficacy endpoint, time-weighted SPID12. This sample size had 90% power to show statistical difference at significant level of 0.05 between two treatment groups. The time-weighted SPID12 is the time- weighted summed pain intensity difference measured over the 12-hour study period. This calculation was based on a two-sided two-sample t-test with a two-to-one sample size allocation ratio and a significance level of α=0.05. Assuming a 10% non-evaluable rate, 180 patients were expected to be randomized to this study.

An intermediate data analysis was planned for this study based on study data collected from approximately 75 patients who had primary efficacy data, time-weighted SPID12. The mean time-weighted SPID12 and its standard deviation (SD) for all patients combined were planned to be calculated based on this intermediate data set without unblinding the randomization treatment codes.

SAP202:

A sample size of approximately 110 patients was planned for this study to ensure at least 100 patients (40 patients in each of two sufentanil NanoTab treatment groups and 20 patients in placebo treatment group) received study drug and have available primary efficacy data for data analysis. A sample size of 60 patients (40 patients in one sufentanil NanoTab treatment group and 20 patients in placebo group) was based on an effect size of 0.8 for the primary efficacy endpoint, time-weighted SPID12. This sample had 80% power to show statistical difference at significant level of 0.05 between two treatment groups. This calculation was based on a two-sided two-sample t-test with two-to-one sample size allocation ratio and a significance level of α = 0.05. To avoid an alpha level correction due to multiple comparisons, the sufentanil NanoTab 30 mcg treatment group was compared to placebo group first, followed by a comparison between the sufentanil NanoTab 20 mcg treatment group and placebo group only if the initial comparison reached a significant level of 0.05. Assuming a 10% non-evaluable rate, a total of 110 patients was expected to be randomized for this study.

- Randomisation

SAP301:
A stratified randomization was applied in this study with sex as a stratification factor. Patients who met the eligibility requirements were randomly assigned, at a 2:1 ratio, into the sufentanil 30 mcg treatment group or placebo treatment group within one of two groups (male or female) at each study centre.

SAP202:
Patients who were deemed eligible for study participation were randomized at a 2:2:1 allocation ratio to receive sufentanil NanoTab 20 mcg, sufentanil NanoTab 30 mcg, or placebo NanoTab during the 12-hour study period. Randomization was stratified within each site to 2 age groups: 18 to 64 years and 65 to 80 years. An IWRS was used to assign the treatment for each patient. Patients were assigned the next available treatment within their strata at the time of randomization.

- **Blinding (masking)**

SAP301:
This was a double-blind study. AcelRx, the Investigator, other study centre personnel, and patients were blinded to treatment group assignment. Study drug for both treatments were identical in appearance.

SAP202:
The active and placebo NanoTabs were identical in appearance so that the Investigator and other study staff, the patients, and the Sponsor were all blinded to treatment group assignment.

- **Rescue Medications**

SAP301:

Rescue medication (1 mg IV morphine) could be given if the patient requested additional medication for pain beyond the use of the study drug. However patients with inadequate analgesia were encouraged to remain in the study without the use of rescue medication for at least 60 minutes after the first dose of study drug. The patient was to first receive a dose of study drug if it had been at least 1 hour since the previous dose of study drug. After 10 minutes, if the patient was still requesting additional medication for pain, rescue medication (1 mg of IV morphine) could be given to the patient. If a dose of study drug had been given within 60 minutes, rescue medication could be given for pain once 10 minutes had passed since dosing with study drug. PI and PR scores must have been taken prior to all doses of rescue medication, in addition to the scores that were required at the specified time points based on when the first dose of study drug was given.
Rescue medications were to be delivered as a slow IV push by an HCP. Patients could not receive a dose of rescue medication more frequently than once every 60 minutes. If a patient continued to have pain that was not controlled by the use of study drug or rescue medication, then the patient was to be discontinued from the study and an alternate form of post-operative analgesia per standard practice at the site was instituted.

SAP202:

Patients with inadequate analgesia were encouraged to remain in the study without the use of rescue medication (Vicodin [5 mg hydrocodone/500 mg acetaminophen]) for at least 60 minutes after the first dose of study medication. Patients were not allowed to use rescue medication until 10 minutes after any dose of study medication, and there was to be at least 4 hours between doses of rescue medication. A patient who received rescue medication was to keep receiving study medication (to be dosed with study drug at least 10 minutes prior to additional doses of rescue medication) and continue in the study with protocol-specified efficacy and safety measures collected.

- **Statistical methods**

Both studies:

The primary null hypothesis to be tested was that the treatment difference in the least squares (LS) mean of the time-weighted SPID12 between each sufentanil NanoTab treatment group and placebo treatment group equals zero.

The statistical tests for the analysis of primary efficacy endpoint were performed at the α = 0.05 significance level. The statistical tests used for the analysis of baseline variables and secondary efficacy endpoints were performed at the α = 0.05 significance level. All tests are two-sided.

Study population analysed:

All randomized patients are those who were randomized to receive the study patient number and treatment assignment.

The intent-to-treat (ITT) population was defined for the analysis of the primary and secondary efficacy variables and included randomized patients who received study medication in studies:

- SAP301: A total of 163 patients were randomized and 161 received study drug and were included in the ITT and safety populations,
- SAP202:. A total of 101 patients were randomized into the study, and 100 patients received study medication. One randomized patients did not receive study medication. A total of 100 randomized patients were considered as ITT patients for the analysis of the primary efficacy variable;

The Completers population was defined for analysis of primary and secondary efficacy variables and included those ITT patients in studies

- SAP301 who completed at least the 24-hour study period per protocol (n=143 patients).
- SAP202 who completed the 12-hour study period per protocol (n=91);

The analysis of efficacy data was based on the randomized treatment group, which was assigned to each patient.

The safety population included all randomized patients who received at least one dose of study drug. The summaries and analyses of safety data were based on the actual treatment that patients received during the treatment period.

Analysis of primary and secondary efficacy variables:

The main analysis of the primary and secondary efficacy variables included the intent-to-treat (ITT) population.

Rescue medication

The PI collected after a patient received the first dose of rescue medication was included in the calculation of the primary efficacy endpoint, time-weighted SPID12.

SAP301:
For patients who used any rescue medication during the study period, the last observed pain data (PI or PR) prior to taking each dose of rescue medication was carried throughout a one-hour time interval following the dosing of rescue medication.

SAP202:
For patients who used any rescue medication during the 12-hour study period, the last observed PI prior to using each dose of rescue medication was carried throughout a follow-up 4-hour time interval. Any PI collected within 4-hour after the start of any rescue medication was excluded from the calculation of the primary efficacy endpoint, time-weighted SPID12.

Imputations

The main analysis of the primary and secondary efficacy endpoints included the ITT population. The ITT population included all randomized patients who received study medication. For patients missing pain intensity or PR data, the following methods were applied to impute the missing data at evaluation time points for the study period:

SAP301:
(1) Missing data were first imputed on a patient-by-patient basis using the linear interpolation method between two observed pain scale values.
(2) For patients who used any rescue medication during the study period, the last observed pain data (PI or PR) prior to taking each dose of rescue medication was carried throughout a one-hour time interval following the dosing of rescue medication.

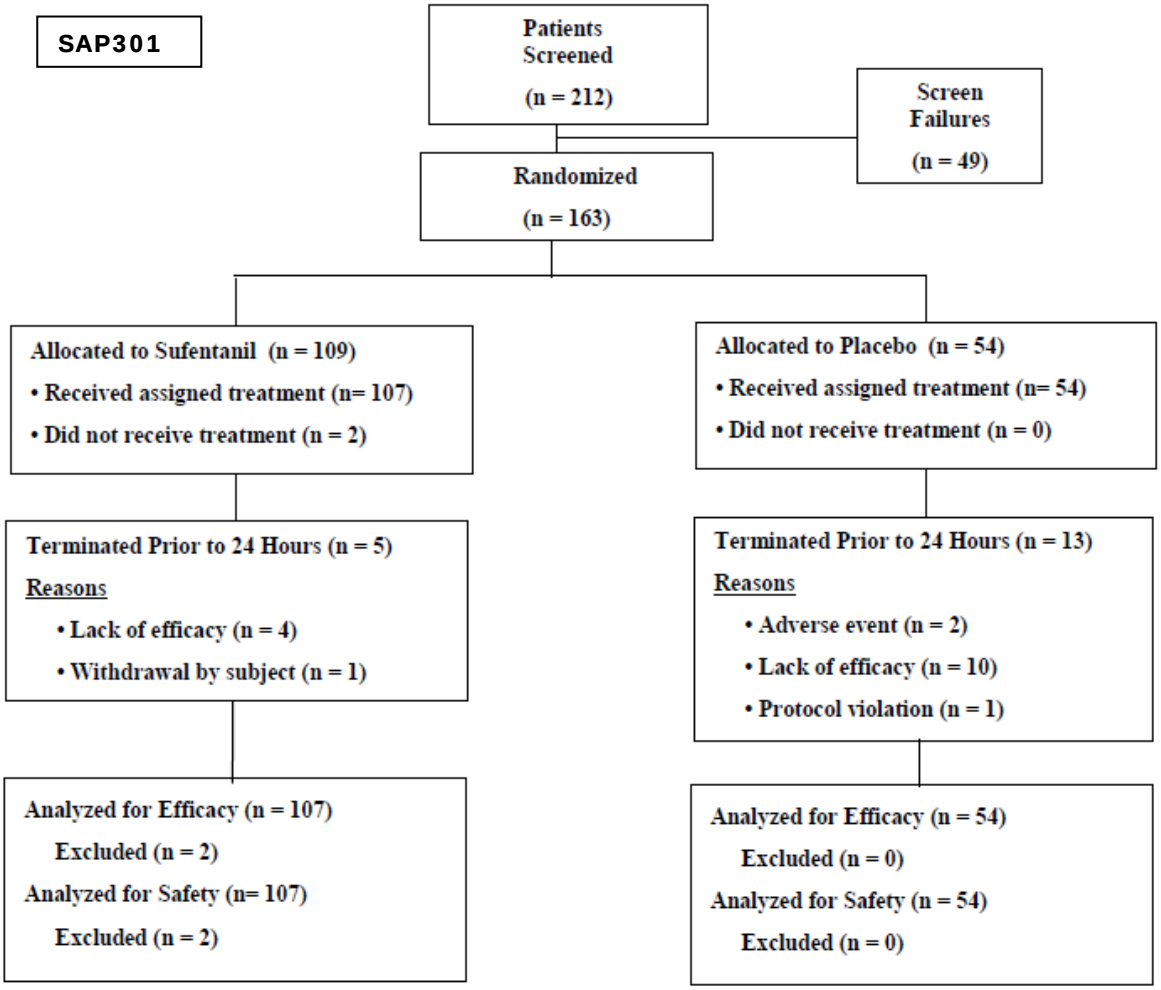
(3) Missing pain data at follow-up time points post-termination up to the end of the study period were imputed on a patient-by-patient basis.

SAP202:
(1) Missing data were first imputed on a patient-by-patient basis using linear interpolation method between two observed pain scale values.
(2) Missing data after a patient terminated from the study or any missing follow-up data after last available data prior to the end of the study period, the pain scale values at follow-up time points post-termination up to the end of the study period were imputed on a patient-by-patient basis as described below.

The last observation carried forward (LOCF) method was used to impute any remaining missing data points after termination due to reasons other than AE up to the end of the study period. For patients who prematurely terminated from the study due to AE, the worst observation carried forward (WOCF) method was used to impute the remaining missing data points up to the end of the study period.

Results

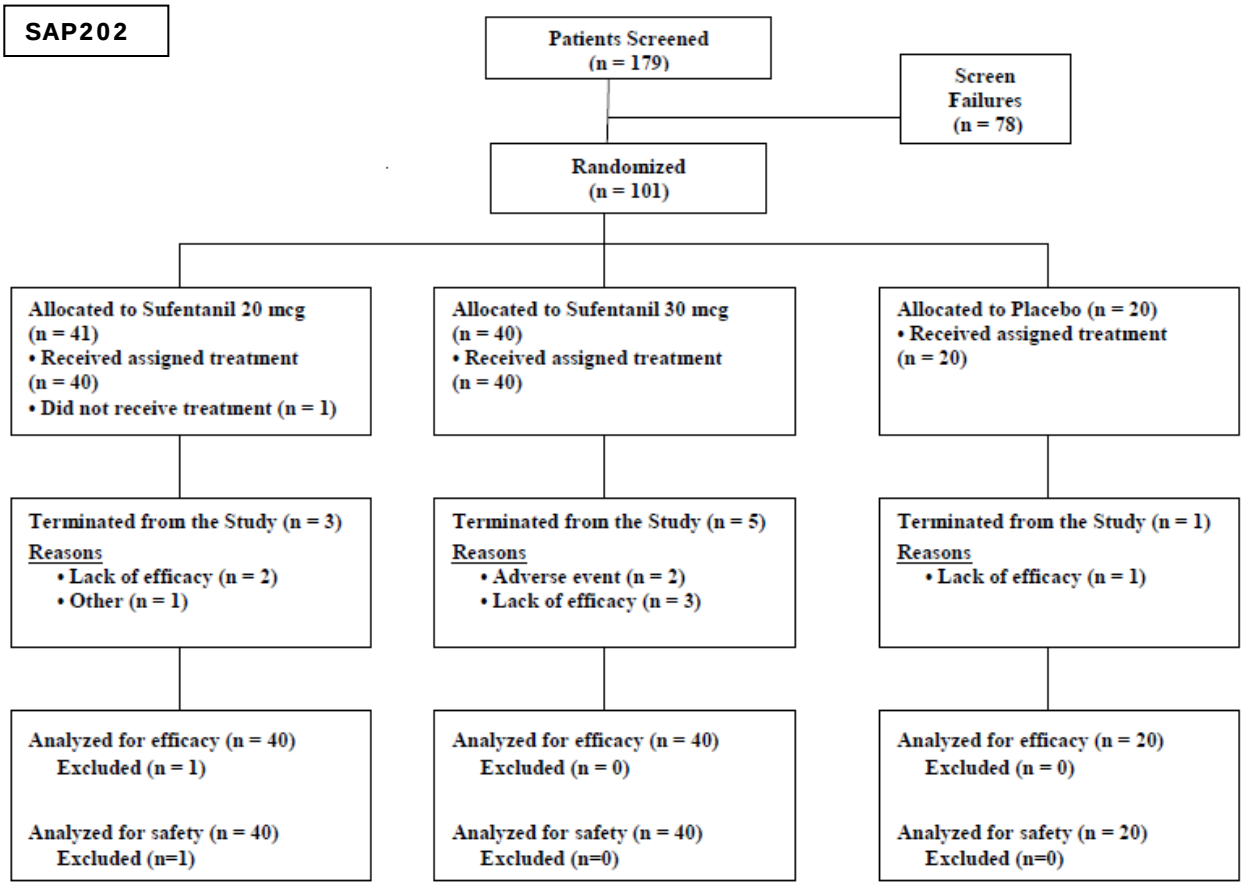
- **Participant flow and numbers analysed**



A total of 212 patients were screened; 49 patient failed screening leaving 163 patients enrolled and randomized in this study. Two patient (sufentanil arm) did not receive study drug, leaving 107 patients in the sufentail arm and 54 in the placebo arm comprising the ITT and safety populations. in total 161 patients (107: 54 in the sufentanil:placebo arms) completed the study and were included in the analysis of primary efficacy endpoint for Completers.

Most common reason of study termination was lack of efficacy (4, 10, respectively in the sufentanil vs placebo arms). Two patients in the placebo arm terminated the study due to adverse events.

SAP202



A total of 179 patients were screened; 78 patients failed screening leaving 101 patients enrolled and randomized in this study. One patient (20 µg sufentanil arm) did not receive study drug, leaving 100 patients (40, 40 and 20 patients in the 20 µg, 30 µg and placebo arms respectively) receiving study drug and comprising the ITT and safety populations. Ninety-one patients [37 (92.5%), 35 (87.5%) and 19 (95%), respectively)] completed the study and were included in the analysis of primary efficacy endpoint for Completers.

Most common reason of study termination was lack of efficacy (2, 2 and 1, respectively in the three arms). Two patients in the 30 µg sufentanil arm terminated the study due to adverse events.

- **Recruitment**

SAP301:
Date first patient enrolled: 10 March 2015
Date last patient completed: 23 June 2015

SAP202:
Date first patient enrolled: 19 October 2012
Date last patient completed: 15 February 2013

- **Conduct of the study**

Amendments:

SAP301: There were 3 amendments (11 Aug 2014 to 20 Jan 2015)

- Study procedures and study visits;
- Dosing of rescue medication

SAP202: There were 6 amendments of study (08 Aug 2011 to 08 Oct 2012). Most of these clarified:

- Study procedures and study visits;
- Definition of Clinically relevant respiratory depression (CRRD);
- Exclusion and withdrawal criteria related to respiratory depression (incl. SpO2 maintained above 95% instead of > 90%).

Protocol deviations:

SAP301: There were several deviations that resulted in the adjustment of data:

• Patients excluded from the analysis of efficacy and safety due to wrong stratification factor (One sufentanil arm) or patient randomized but not dosed (2 sufentanil arm)

• Data adjusted for the derivation of efficacy outcome variable due to

missing PI and/ or PR data (9 sufentanil, 7 placebo)

PGA /HPGA not completed (19 sufentanil, 15 placebo)

• Missing baseline SpO2 data (3 sufentanil). Excluded from by-visit summary of SpO2 data.

SAP202: There were 9 major protocol deviations. Five of these resulted in adjustment of data analysis:

• One patient (sufentanil 20 mcg group) was randomized to treatment but not dosed due to residue found inside the treatment bottle. This patient was excluded from the ITT analysis of efficacy and safety data analyses

• Four patients (1 in sufentanil 20 mcg group, 3 in sufentanil 30 mcg group) had missing pain intensity/relief data. Adjusted for the derivation of efficacy outcome variables.

No action was taken for other types of deviations, which include deviations from rescue medication, missing PGA data, withdrawal criteria and medication kit error.

- **Baseline data**

SAP301:

	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	Total (n = 161)
Age (years): n (%)			
< 65	106 (99.1%)	53 (98.1%)	159 (98.8%)
≥ 65	1 (0.9%)	1 (1.9%)	2 (1.2%)
Mean (SD)	41.2 (10.6)	40.4 (12.1)	40.9 (11.1)
Min, max	18.0, 69.0	20.0, 68.0	18.0, 69.0
Sex: n (%)			
Male	34 (31.8%)	18 (33.3%)	52 (32.3%)
Female	73 (68.2%)	36 (66.7%)	109 (67.7%)
Race: n (%)			
White	76 (71.0%)	37 (68.5%)	113 (70.2%)
Black or African American	21 (19.6%)	10 (18.5%)	31 (19.3%)
Asian	3 (2.8%)	1 (1.9%)	4 (2.5%)
Other	7 (6.5%)	6 (11.1%)	13 (8.1%)
Ethnicity: n (%)			
Hispanic or Latino	42 (39.3%)	19 (35.2%)	61 (37.9%)
Not Hispanic or Latino	65 (60.7%)	35 (64.8%)	100 (62.1%)
Body Mass Index (kg/m^2) : n (%)			
< 30	77 (72.0%)	35 (64.8%)	112 (69.6%)
≥ 30	30 (28.0%)	19 (35.2%)	49 (30.4%)
Mean (SD)	27.5 (4.8)	27.6 (4.9)	27.5 (4.8)
Min, max	18.0, 42.0	15.8, 39.2	15.8, 42.0
Surgery: n (%)			
Abdominoplasty	52 (48.6%)	28 (51.9%)	80 (49.7%)
Hernioplasty	23 (21.5%)	10 (18.5%)	33 (20.5%)
Laparoscopic abdominal surgery	32 (29.9%)	16 (29.6%)	48 (29.8%)

Source: Table 14.1.10.

SD: standard deviation; ITT: intent-to-treat.

SAP202:

	Sufentanil 20 mcg (n = 40)	Sufentanil 30 mcg (n = 40)	Placebo (n = 20)	Total (n = 100)
Age (years) - n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
< 65	39 (97.5%)	38 (95.0%)	19 (95.0%)	96 (96.0%)
≥ 65	1 (2.5%)	2 (5.0%)	1 (5.0%)	4 (4.0%)
Mean (SD)	42.5 (12.6)	43.0 (12.5)	41.7 (13.6)	42.5 (12.6)
Median	41.5	44.0	40.5	43.0
Min, max	(18.0, 76.0)	(18.0, 74.0)	(21.0, 72.0)	(18.0, 76.0)
Sex- n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
Male	21 (52.5%)	20 (50.0%)	10 (50.0%)	51 (51.0%)
Female	19 (47.5%)	20 (50.0%)	10 (50.0%)	49 (49.0%)
Race- n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
American Indian or Alaska Native	1 (2.5%)	0 (0%)	0 (0%)	1 (1.0%)
Asian	2 (5.0%)	1 (2.5%)	1 (5.0%)	4 (4.0%)
Black or African American	7 (17.5%)	12 (30.0%)	4 (20.0%)	23 (23.0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (2.5%)	0 (0%)	1 (1.0%)
White	30 (75.0%)	26 (65.0%)	15 (75.0%)	71 (71.0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity - n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
Hispanic or Latino	8 (20.0%)	5 (12.5%)	4 (20.0%)	17 (17.0%)
Not Hispanic or Latino	32 (80.0%)	35 (87.5%)	16 (80.0%)	83 (83.0%)
ASA Classification – n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
I	28 (70.0%)	28 (70.0%)	14 (70.0%)	70 (70.0%)
II	11 (27.5%)	12 (30.0%)	6 (30.0%)	29 (29.0%)
III	1 (2.5%)	0 (0%)	0 (0%)	1 (1.0%)
Body Mass Index (kg/m2) - n (%)	40 (100%)	40 (100%)	20 (100%)	100 (100%)
< 30	25 (62.5%)	28 (70.0%)	13 (65.0%)	66 (66.0%)
≥ 30	15 (37.5%)	12 (30.0%)	7 (35.0%)	34 (34.0%)
Mean (SD)	28.4 (6.2)	28.5 (7.3)	26.9 (4.2)	28.2 (6.3)
Median	26.9	26.9	27.4	27.1
Min, max	(20.4, 47.1)	(17.7, 53.5)	(19.6, 33.5)	(17.7, 53.5)

Source: Post-text Table 14.1.5
ITT: intent-to-treat; max: maximum; min: minimum; SD: standard deviation.

- **Outcomes and estimation**

SAP202

Primary efficacy endpoint – SPID12

	Sufentanil 20 mcg (n = 40)	Sufentanil 30 mcg (n = 40)	Placebo (n = 20)	Overall Treatment P-value[1]
Baseline Pain Intensity				
Mean (SD)	6.45 (1.28)	6.48 (1.45)	6.00 (1.12)	
LS Mean (SEM)	6.44 (0.21)	6.48 (0.21)	5.98 (0.30)	0.353
95% CI	(6.03, 6.86)	(6.07, 6.90)	(5.40, 6.57)	
p-value (vs. placebo)[2]	0.209	0.173		
Time-weighted SPID12				
Mean (SD)	-5.26 (17.72)	7.29 (18.00)	-9.64 (18.45)	
LS Mean (SEM)	-5.65 (2.55)	6.53 (2.56)	-7.12 (3.64)	0.001
95% CI	(-10.72, -0.58)	(1.46, 11.61)	(-14.35, 0.11)	
p-value (W)[3]	0.029	0.012	0.053	
Difference[3]				
LS Mean Difference (SEM)	1.47 (4.45)	13.66 (4.47)	NA	
95% CI for Difference	(-7.37, 10.31)	(4.79, 22.52)		
p-value (vs. placebo)[4]	0.742	0.003		

Source: Post-text Table 14.2.1.

ITT: intent-to-treat; CI: confidence interval; LS: least squares; NA: not applicable; SD: standard deviation; SEM: standard error of LS mean.

For the baseline pain intensity (PI), the LS mean and SEM were estimated from the ANOVA model that included treatment and center factors.

For the time-weighted SPID12, the LS mean and SEM were estimated from the ANCOVA model that included treatment and center factors, and baseline PI as a covariate.

[1]The p-value (overall) for the overall comparison among all treatment groups was based on Type III analysis from the models described above.

[2]The p-value (vs. placebo) for the pairwise test of difference of the LS mean between two groups was based on the t-test of Type III analysis from the models described above.

[3]Sufentanil minus placebo.

[4]The p-value (W) for the test of LS mean within each group was based on Type III analysis from the models described above.

Secondary efficacy endpoints SPID1 and TOTPAR12

SPID1

	Sufentanil 20 mcg (n = 40)	Sufentanil 30 mcg (n = 40)	Placebo (n = 20)	Overall Treatment P-value[1]
Time-weighted SPID1				
Mean (SD)	0.52 (1.39)	1.66 (1.51)	0.05 (1.59)	
LS Mean (SEM)	0.49 (0.23)	1.64 (0.23)	0.15 (0.32)	<0.001
95% CI	(0.04, 0.94)	(1.19, 2.09)	(-0.49, 0.78)	
p-value (W)[2]	0.034	<0.001	0.653	
Difference[3]				
LS Mean Difference (SEM)	0.34 (0.39)	1.49 (0.40)	NA	
95% CI for Difference	(-0.44, 1.12)	(0.71, 2.28)		
p-value (vs. placebo)[4]	0.388	<0.001		

Source: Post-text Table 14.2.4.

ITT: intent-to-treat; CI: confidence interval; LS: least squares; NA: not applicable; SD: standard deviation; SEM: standard error of LS mean.

For the time-weighted SPID1, the LS mean and SEM were estimated from the ANCOVA model that included treatment and center factors, and baseline PI as a covariate.

[1] The p-value (overall) for the overall comparison among all treatment groups was based on Type III analysis from the models described above.

[2] The p-value (W) for the test of LS mean within each group was based on Type III analysis from the models described above.

[3] Sufentanil minus placebo.

[4] The p-value (vs. placebo) for the pairwise test of difference of the LS mean between two groups was based on the t-test of Type III analysis from the models described above.

	Sufentanil 20 mcg (n = 40)	Sufentanil 30 mcg (n = 40)	Placebo (n = 20)	Overall Treatment P-value[1]
TOTPAR12				
Mean (SD)	4.76 (5.50)	9.77 (7.23)	4.30 (5.06)	
LS Mean (SEM)	4.74 (0.96)	9.63 (0.97)	4.71 (1.38)	0.001
95% CI	(2.82, 6.65)	(7.72, 11.55)	(1.98, 7.44)	
p-value (W)[2]	<0.001	<0.001	0.001	
Difference[3]				
LS Mean Difference (SEM)	0.03 (1.68)	4.93 (1.69)	NA	
95% CI for Difference	(-3.31, 3.37)	(1.58, 8.28)		
p-value (vs. placebo)[4]	0.985	0.004		

Source: Post-text Table 14.2.6.

ITT: intent-to-treat; CI: confidence interval; LS: least squares; max: NA: not applicable; SD: standard deviation; SEM: standard error of LS mean.

For the TOTPAR12, the LS mean and SEM were estimated from the ANCOVA model that included treatment and center factors, and baseline PI as a covariate.

[1] The p-value (overall) for the overall comparison among all treatment groups was based on Type III analysis from the models described above.

[2] The p-value (W) for the test of LS mean within each group was based on Type III analysis from the models described above.

[3] Sufentanil minus placebo.

[4] The p-value (vs. placebo) for the pairwise test of difference of the LS mean between two groups was based on the t-test of Type III analysis from the models described above.

Both studies

Primary Endpoint – Time-weighted SPID12

Time-weighted SPID12	Sufentanil 30 mcg	Placebo
SAP301	n = 107	n = 54
LS mean (SEM)	25.84 (1.71)	13.14 (2.35)
95% CI	(22.46, 29.22)	(8.50, 17.79)
LS mean difference[a] (SEM)	12.70 (2.80)	NA
p-value (vs. placebo)[b]	< 0.001	
SAP202	n = 40	n = 20
LS Mean (SEM)	5.93 (2.50)	-6.72 (3.57)
95% CI	(0.96, 10.90)	(-13.80, 0.36)
p-value (W)[c]	0.020	0.063
LS mean difference[a] (SEM)	12.65 (4.38)	NA
p-value (vs. placebo)[b]	0.005	

Abbreviations: LS = least squares; NA = not applicable; SEM = standard error of the LS mean; SPID12 = summed pain intensity difference over the 12-hour study period.
[a] Sufentanil minus placebo.
[b] P-value for the test of treatment effect is based on Type III analysis from the models described.
[c] The p-value (W) for the test of LS mean within each group was based on Type III analysis from the models described.
Notes: For the baseline pain intensity, the LS mean and SEM were estimated from the ANOVA model that included treatment, center, and sex factors for SAP301 and treatment and center factors for SAP202. For the time-weighted SPID12, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and sex factors for SAP301 and treatment and center factors for SAP202, and baseline pain intensity as a covariate.

Key Secondary Endpoints:

In addition to the primary SPID results, key secondary endpoint results support the efficacy of SST 30 mcg. In the placebo-controlled studies, superiority of SST 30 mcg versus placebo was demonstrated for nearly all measures, including pain assessments, patient and HCP satisfaction measures, time to perceptible pain relief, and rescue/supplemental opioid use.

	SST 30 mcg	Placebo	P-value[a]
Study SAP301			
Time-weighted SPID1; LS mean (SEM)	1.09(0.15)	-0.37(0.21)	< 0.001[b]
Time-weighted SPID24; LS mean (SEM)	57.96(3.45)	37.28(4.75)	< 0.001[b]
Time-weighted SPID48; LS mean (SEM)	67.51 (4.31)	45.74 (5.93)	0.002[b]
Time-weighted TOTPAR12; LS mean (SEM)	21.18(0.87)	15.36(1.19)	< 0.001[b]
Time-weighted TOTPAR24; LS mean (SEM)	45.80(1.81)	35.45(2.49)	0.001[b]
Time-weighted TOTPAR48; LS mean (SEM)	67.68(2.28)	56.67(3.14)	0.004[b]
Time-weighted SPRID12; LS mean (SEM)	47.03(2.35)	28.62(3.24)	< 0.001[b]
Time-weighted SPRID24; LS mean (SEM)	103.88(4.81)	73.05(6.62)	< 0.001[b]
Time-weighted SPRID48; LS mean (SEM)	135.56 (6.04)	102.87 (8.31)	0.001[b]
Proportion of patients responding good or excellent on PGA24; n (%)	86 (80.4%)	28 (51.9%)	< 0.001[c]
Proportion of patients responding good or excellent on PGA48; n (%)	94 (87.9%)	28 (51.9%)	< 0.001[c]
Proportion of HCPs responding good or excellent on HPGA24; n (%)	86 (80.4%)	29 (53.7%)	< 0.001[c]
Proportion of HCPs responding good or excellent on HPGA48; n (%)	89 (83.2%)	30 (55.6%)	< 0.001[c]
Patients who terminated due to inadequate analgesia during the 24-hour study period; n (%)	4 (3.7%)	10 (18.5%)	0.002[c]
Time to termination due to inadequate analgesia over the 24-hour study period			0.001[d]
Time to termination due to inadequate analgesia over the entire study period			0.001[d]
Patients who took rescue medication due to inadequate analgesia; n (%)	29 (27.1%)	35 (64.8%)	< 0.001[c]
Time to take first rescue medication due to inadequate analgesia over the 12-hour study period			< 0.001[d]
Time to perceptible pain relief; median minutes	24	78	0.002[d]
Time to meaningful pain relief; median minutes	54	84	0.156[d]
Number of Morphine Doses Used from 0 - 6 Hours; Mean (SD)	0.3 (0.7)	1.1 (1.1)	< 0.001[e]
Number of Morphine Doses Used from 0 - 12 Hours; Mean (SD)	0.4 (1.0)	1.6 (1.8)	< 0.001[e]
Number of Morphine Doses Used from 0 - 24 Hours; Mean (SD)	0.5 (1.4)	2.1 (2.9)	< 0.001[e]
Total Morphine Doses Used for Entire Study Period; Mean (SD)	0.6 (1.6)	2.4 (3.7)	0.001[e]
Number of Morphine Doses per Hour from 0 – 6 Hours; Mean (SD)	0.05 (0.12)	0.18 (0.19)	< 0.001[e]
Number of Morphine Doses per Hour from 0 – 12 Hours; Mean (SD)	0.03 (0.08)	0.13 (0.15)	< 0.001[e]
Number of Morphine Doses per Hour from 0 – 24 Hours; Mean (SD)	0.02 (0.06)	0.09 (0.12)	< 0.001[e]
Total Morphine Doses per Hour; Mean (SD)	0.01 (0.03)	0.05 (0.08)	0.001[e]
Study SAP202			
Time-weighted SPID1; LS mean (SEM)	1.64 (0.23)	0.15 (0.32)	< 0.001[b]
Time-weighted TOTPAR12; LS mean (SEM)	9.64 (0.96)	4.67 (1.37)	0.001[b]
Pain intensity, 1 hour; LS mean (SEM)	4.10 (0.30)	6.48 (0.43)	< 0.001
PID, 1 hour; LS mean (SEM)	2.27 (0.30)	-0.11 (0.43)	< 0.001

	SST 30 mcg	Placebo	P-value[a]
PR, 1 hour; LS mean (SEM)	1.67 (0.15)	0.48 (0.22)	< 0.001
PRID, 1 hour; LS mean (SEM)	3.93 (0.44)	0.36 (0.63)	< 0.001
Proportion of patients responding good or excellent on PGA for effectiveness; n (%)	17 (43.6%)	1 (5.0%)	0.002[c]
Patients who terminated the study due to inadequate analgesia during the 24-hour study period; n (%)	3 (7.5%)	1 (5.0%)	0.714[c]
Patients who took rescue medication due to inadequate analgesia; n (%)	28 (70.0%)	20 (100.0%)	0.006[c]
Time to take the first rescue medication due to inadequate analgesia; median minutes	319	128	< 0.001[d]
Time to perceptible pain relief; median minutes	29	NA	0.019[d]
Time to meaningful pain relief; median minutes	78	NA	0.016[d]
Total Rescue Doses Used for Entire Study Period; Mean (SD)	1.1 (0.9)	2.1 (0.7)	< 0.001[f]

Abbreviations: CI = confidence interval; HCP = healthcare professional; HPGA24/48 = healthcare professional global assessment of method of pain control at 24/48 hours; ITT = intent-to-treat; LS = least squares; NA = not applicable; PGA24/48 = patient global assessment of method of pain control at 24/48 hours; SD = standard deviation; SEM = standard error of the LS mean; SPID1/24/48 = summed pain intensity difference over the 1-, 24- and 48-hour study periods; SPRID12/24/48 = summed pain relief intensity difference over the 12-, 24-, and 48-hour study periods; TOTPAR12/24/48 = total pain relief over the 12-, 24- and 48-hour study periods.

[a] The p-values are for comparison of SST 30 mcg and placebo, unless otherwise noted

[b] The p-value for the test of treatment effect is based on Type III analysis from the model described.

[c] The p-value based on Z test for the difference in proportions between 2 groups.

[d] The p-value based on the log-rank test.

[e] The p-value is based on the 2 sample t-test for numeric data or a 2-sided Fisher's exact test for categorical data.

[f] The p-value is for the overall comparison among all 3 treatment groups in SAP202 (SST 30 mcg, SST 20 mcg, and placebo) and is based on the F-test of Type III treatment factor from the ANOVA model including only the treatment factor for numeric data or a 2-sided Fisher's exact test for categorical data.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3. Summary of Efficacy for trial SAP202

Title: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® for the Management of Acute Pain Following Bunionectomy Alone or with Hammertoe Repair		
Study identifier	**SAP 202**	
Design	The study was a multicentre, randomized, double-blind, placebo-controlled trial for 12 hours in patients 18 to 80 years of age who were undergoing bunionectomy alone or with hammertoe repair.	
	Duration of main phase:	12 hours
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	

Treatments groups	Sufentanil NanoTab 20µg		Sufentanil 20µg tablet N=40
	Sufentanil NanoTab 30µg		Sufentanil 30µg tablet N=40
	Placebo NanoTab		Placebo N=20
Endpoints and definitions	Primary endpoint	SPID12	Time-weighted summed pain intensity difference (SPID) over the 12-hour study period.
	Secondary endpoints	SPID1	Time-weighted summed pain intensity difference over the first hour
		SPID by evaluation time point	Time-weighted summed pain intensity difference by evaluation time point (30 minutes after the administration)
		TOTPAR12	Total pain relief (TOTPAR) over the 12 hours of the study period
		TOTPAR by evaluation time point	Total pain relief by evaluation time point
		PI, PID, PR, PRID	Pain intensity (PI) and pain intensity difference (PID), pain relief (PR), and pain relief intensity difference (PRID) at each evaluation time point
		PGA	Patient global assessment of method of pain control (effectiveness and tolerability)
			Proportion of patients who terminated from the study due to inadequate analgesia
			Rescue medication use due to inadequate analgesia
			Time to onset of perceptible and meaningful pain relief
			Total number of study drug doses used
			Interdosing interval
			Use of observed pain data

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 12 hours			
Descriptive statistics and estimate variability	Treatment group	Sufentanil NanoTab 20µg	Sufentanil NanoTab 30µg	Placebo Nanotab
	Number of subject	40	40	20
	SPID12 LS Mean (SEM)	-5.65 (2.55)	6.53 (2.56)	-7.12 (3.64)
	95% CI	(-10.72, -0.58)	(1.46, 11.61))	(-14.35, 0.11)
	SPID1 LS Mean (SEM)	0.49 (0.23)	1.64 (0.23)	0.15 (0.32)
	TOTPAR12 LS Mean (SEM)	4.74 (0.96)	9.63 (0.97)	4.71 (1.38)
	PI 1 hour LS Mean (SEM)		4.1 (0.30)	6.48 (0.43)

	PID 1 hour LS Mean (SEM)		2.27 (0.30)	-0.11 (0.43)
	PR 1 hour LS Mean (SEM)		1.67 (0.15)	0.48 (0.22)
	PRID 1 hour LS Mean (SEM)		3.93 (0.44)	0.36 (0.63)
	Proportion of patients responding good or excellent on PGA for effectiveness; n (%)	4 (10%)	17 (43.6%)	1 (5.0%)
	Proportion of patients who terminated from the study due to inadequate analgesia 24h; n (%)	2 (5.0)	3 (7.5%)	1 (5.0%)
	Patients who took rescue medication due to inadequate analgesia; n (%)	39 (97.5%)	28 (70%)	20 (100%)
	Time to take the first rescue medication due to inadequate analgesia; median minutes	185	319	128
	Rescue medication use due to inadequate analgesia; Mean (SD)	1.8 (0.9)	1.1 (0.9)	2.1 (0.7)

Effect estimate per comparison	SPID12 LS Mean difference	Comparison groups	Sufentanil 30µg - placebo
		LS Mean difference	13.66
		95% CI for difference	4.79, 22.52
		P-value	0.003
	SPID 1	SEM	
		P-value	<0.001
	TOTPAR12	SEM	9.63 (0.97) 4.71 (1.38)
		P-value	<0.001
	PI 1 hour	SEM	4.1 (0.30)
		P-value	<0.001
	PID 1 hour	SEM	2.27 (0.30)
		P-value	<0.001
	PR 1 hour	SEM	1.67 (0.15)
		P-value	<0.001

	PRID 1 hour	SEM	3.93 (0.44) 0.36 (0.63)
		P-value	<0.001
	Proportion of patients responding good or excellent on PGA for effectiveness	%	17 (43.6%)
		P-value	0.002
	Proportion of patients who terminated from the study due to inadequate analgesia 24h	%	3 (7.5%)
		P-value	0.714
	Patients who took rescue medication due to inadequate analgesia	SEM	28 (70%) 20 (100%)
		P-value	0.006
	Time to take the first rescue medication due to inadequate analgesia; median minutes	Median minutes	319
		P-value	<0.001
	Rescue medication use due to inadequate analgesia	SD	1.1 (0.9)
		P-value	<0.001

Table 4. Summary of Efficacy for trial 301

Title: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sublingual Sufentanil Tablet 30 µg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery			
Study identifier	**SAP 301**		
Design	The study was a multicentre, randomized double-blind, placebo-controlled trial in adult patients who had undergone an ambulatory abdominal surgery normally performed as an outpatient procedure: abdominoplasty; open-tension-free inguinal hernioplasty (Lichtenstein repair with mesh); or laparoscopic abdominal surgery.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 hours not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Sufentanil NanoTab 30µg		Sufentanil 30µg tablet N=107
	Placebo NanoTab		Placebo N=54
Endpoints and definitions	Primary endpoint	SPID12	Time-weighted summed pain intensity difference (SPID) over the 12-hour study period.
	Secondary endpoints	SPID1	Time-weighted summed pain intensity difference over the first hour

		SPID24	Time-weighted summed pain intensity difference over 24 hours
		SPID48	Time-weighted summed pain intensity difference over 48 hours
		TOTPAR12	Total pain relief (TOTPAR) over the 12 hours of the study period
		TOTPAR24	Total pain relief (TOTPAR) over the 24 hours of the study period
		TOTPAR48	Total pain relief (TOTPAR) over the 48 hours of the study period
		SPRID12, SPRID24, SPRID48	Time-weighted summed pain relief intensity difference (SPRID) over the 12, 24, and 48 hours of the study period
		PGA	Patient global assessment of method of pain control (effectiveness and tolerability)
			Proportion of patients who terminated from the study due to inadequate analgesia
			Rescue medication use due to inadequate analgesia
			Time to onset of perceptible and meaningful pain relief
			Total number of study medication and rescue medication doses used over the 48-hour study period
			Mean duration of inter-dosing interval over the 12, 24, and 48 hours of the study period
			Time to first use of rescue medication

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 12 hours		
Descriptive statistics and estimate variability	Treatment group	Sufentanil NanoTab 30µg	Placebo Nanotab
	Number of subject	107	54
	SPID12 LS Mean (SEM)	25.84 (1.71)	13.14 (2.35)
	95% CI	22.46, 29.22	8.50, 17.79
	SPID1 LS Mean (SEM) 95% CI	1.09 (0.15) 0.73, 1.39	-0.37 (0.21) -0.78, 0.04
	SPID24 LS Mean (SEM) 95% CI	57.96 (3.45) 51.15, 64.78	37.28 (4.75) 27.91, 46.66
	SPID48 LS Mean (SEM) 95% CI	67.51 (4.31) 58.99, 76.04	45.74 (5.93) 34.02, 57.46

	TOTPAR12 LS Mean (SEM) 95%CI	21.18 (0.87) 19.48, 22.89	15.36 (1.19) 13.01, 17.71
	TOTPAR24 LS Mean (SEM) 95%CI	45.8 (1.81) 42.23, 49.38	35.45 (2.49) 30.53, 40.37
	TOTPAR48 LS Mean (SEM) 95%CI	67.68 (2.28) 63.17, 72.19)	56.67 (3.14) 50.47, 62.87
	SPRID12 LS Mean (SEM) 95%CI	47.03 (2.35) 42.38, 51.67	28.62 (3.24 22.23, 35.01
	SPRID24 LS Mean (SEM) 95%CI	103.88 (4.81) 94.36, 113.39	73.05 (6.62) 59.96, 86.13
	SPRID48 LS Mean (SEM) 95%CI	135.56 86.04 123.63, 147.51	102.87 (88.27) 86.45, 119.29
	Proportion of patients responding good or excellent on PGA for effectiveness; n (%) PGA24, 95% CI	86 (80.4%) 72.85%, 87.9%	28 (50%) 13.20%, 43.80%
	Proportion of patients responding good or excellent on PGA for effectiveness; n (%) PGA48, 95%CI	94 (87.90%) 81.66%, 94.04%	28 (51.9%) 38.52%, 65.18%
	Proportion of patients who terminated from the study due to inadequate analgesia 24h; n (%)	4 (3.7%)	10 (18.5)
	Patients who took rescue medication due to inadequate analgesia; n (%)	29 (27.1%)	35 (64.8)
	Time to perceptible pain relief; median minutes	24	78
	Rescue medication use due to inadequate analgesia; 24 hours, Mean (SD)	0.5 (1.4)	2.1 (2.9)

Effect estimate per comparison	SPID12 LS Mean difference	Comparison groups	Sufentanil 30µg - placebo
		LS Mean difference	12.70 (2.80)
		95% CI for difference	7.16, 18.23
		P-value	<0.001
	SPID 1	LS Mean difference	1.46 (0.25)
		95% CI for difference	0.97, 1.95
		P-value	<0.001
	SPID24	LS Mean difference	20.68 (5.65)

		95% CI for difference	9.51, 31.85
		P-value	<0.001
	SPID48	LS Mean difference	21.77 (7.07)
		95% CI for difference	7.81, 35.74
		P-value	0.002
	TOTPAR12	LS Mean difference	5.83 (1.42)
		95% CI for difference	3.03, 8.63
		P-value	<0.001
	TOTPAR24	LS Mean difference	10.36 (2.97)
		95% CI for difference	4.50, 16.22
		P-value	0.001
	TOTPAR48	LS Mean difference	11.01 (3.74)
		95% CI for difference	3.62, 18.39
		P-value	0.004
	SPRID12	LS Mean difference	18.41 (3.86)
		95% CI for difference	10.79, 26.02
		P-value	<0.001
	SPRID24	LS Mean difference	30.83 (7.89)
		95% CI for difference	15.24, 46.41
		P-value	<0.001
	SPRID48	LS Mean difference	32.69 (9.90)
		95% CI for difference	13.14, 52.25
		P-value	0.001
	Proportion of patients responding good or excellent on PGA for effectiveness PGA24 difference, 95% CI	difference	28.50%
		95% CI for difference	13.20%, 43.80%
		P-value	<0.001
	Proportion of patients responding good or excellent on PGA for effectiveness PGA48 difference, 95% CI	difference	36.00%
		95% CI for difference	21.31%, 50.69%
		P-value	<0.001
	Proportion of patients who terminated from the study due to inadequate analgesia 24h	%	4 (3.7%)
		P-value	0.002
	Patients who took rescue medication due to inadequate analgesia	%	29 (27.1%) 35 (64.8)
		P-value	<0.001

	Time to perceptible pain relief; median minutes	minutes	24
		P-value	0.002
	Rescue medication use due to inadequate analgesia 24 hours	SD	0.5 (1.4)
		P-value	<0.001

Analysis performed across trials (pooled analyses and meta-analysis)

Data were not integrated across studies because the 2 placebo-controlled Phase 2 and 3 studies used different pain models (abdominal surgery [SAP301] vs. bunionectomy [SAP202]) and the other 2 Phase 3 studies (SAP302 and SAP303) had a different study design (open-label studies). Therefore, integrated data analyses not were performed, and statistical analyses were performed for each study individually.

Due to the heterogeneity of the study designs other than a descriptive comparison cannot be done by pooling the study results. The comparison has been made in the Discussion section of this report.

Supportive studies

Two Phase 3 open-label safety and efficacy studies (SAP302, SAP303) were conducted with SST 30 µg. Study SAP302 enrolled 76 patients with moderate-to-severe acute pain due to injury or trauma in an emergency room (ER) setting with study drug treatment for up to 5 hours, and Study SAP303 enrolled 140 postoperative patients aged 40 years or older who had undergone surgery and were expected to have moderate-to-severe acute pain for at least 12 hours. Study drug was administered to the patient's sublingual space by a qualified HCP using the SDA. Both studies were conducted in the United States.

Table: Phase 3 open-label studies

Study	Study Design	Study Treatment/ Duration	Patient Type
SAP302	Multicenter, open-label	SST 30 mcg; PRN; sublingual/ Up to 5 hours	Emergency room setting – adult patients with pain due to trauma or injury
SAP303	Multicenter, open-label in subjects 40 years or older	SST 30 mcg; PRN; sublingual/ Up to 12 hours	Postsurgical patients 40 years or older following any type of surgery

Abbreviations: PRN = pro re nata (as required); SST = sufentanil sublingual tablet.

The primary efficacy endpoints in each study, SPID1 for SAP302 (ER setting) and SPID12 for SAP303 (orthopedic, abdominal, or other types of surgeries), were clinically significant. Efficacy was further supported by secondary endpoint results, including pain intensity, TOTPAR, PGA, HPGA, use of rescue medication, and dropouts due to inadequate analgesia. In both studies, reductions in pain intensity and/or improvement in pain relief were observed as early as 15 minutes. In addition, a post-hoc responder analysis of SAP302 demonstrates a substantial analgesic response to a single-dose of SST 30 μg within 60 minutes (at 1 hour, a PI reduction $\geq$ 30% was observed for 48.6% of patients and $\geq$ 50% was observed for 36.8% of patients). A clinically meaningful reduction in pain intensity (mean

drop of 2.9 to 5.2, moderate pain [from a mean baseline score of severe pain, 8.1]) was achieved 1 hour after administration of a single SST 30 µg tablet. Furthermore, a reduction in pain intensity of 1.3, previously demonstrated to be clinically significant in ER patients (Bijur 2003), occurred on average within 20 minutes. In SAP303, from a mean baseline score of 6.2, a reduction in pain intensity of 1.7 was achieved by 1 hour and of 3.5 was achieved by 12 hours.

Safety and efficacy data collected and submitted as part of the Zalviso (sufentanil sublingual tablet system; SST 15 µg) clinical development program were used to support the SST 30 µg safety and efficacy assessment. The 3 Zalviso Phase 2 studies and 3 Zalviso Phase 3 studies conducted with SST 15 µg were conducted in patients who had undergone open abdominal, knee-replacement, or hip-replacement surgery.

One of the studies (IAP309) of SST 15 µg compared the efficacy of the SST 15 µg (Zalviso) to IV patient-controlled analgesia (PCA) with morphine sulfate (MS). The IV MS regimen was a standard 1 mg dose, with a 6-minute lockout regimen. The original primary endpoint in this study was the patient global assessment of the method of pain control over the 48-hour duration of the study (PGA48). Zalviso (SST 15 µg no more frequently than every 20 minutes) was both non-inferior as well as superior for treatment effect to IV MS. During scientific advice discussions with several European Health Authorities regarding a planned European marketing authorisation application for SST 30 µg, the Health Authorities recommended re-analyzing the efficacy data from IAP309 by comparing the IV MS group to only those SST 15 μg patients who dosed 30 μg or less ($\leq$ 2 doses of SST 15 μg) per hour. Also, analysis of earlier efficacy endpoints (up to 24 hours) was also requested. These patients represent a reasonable surrogate group for evaluating the efficacy of SST 30 µg versus a standard of care for treatment of severe pain (IV MS). The dosing of IV MS in this IAP309 study (a median use of 10 mg IV within the first 3 hours) reflects typical dosing of IV MS in both the post-operative setting, as well as other settings in which IV MS is administered as an IV bolus by an HCP, such as in the ER.

Similar to the original Phase 3, active-controlled study IAP309 results which demonstrated both non-inferiority as well as superiority of treatment effect of SST 15 µg compared to a standard IV PCA MS regimen (1 mg morphine; 6 minute lockout) based on the pre-defined primary endpoint of PGA48 (Study IAP309 CSR), results of the re-analysis (IAP309 Addendum) showed that SST $\leq$ 30 μg/hour was at least as effective over 24 hours as IV MS for the management of acute post-operative pain in patients who had undergone major abdominal or orthopedic surgery. For the primary efficacy endpoint in the re-analysis (good or excellent response on the PGA24), non-inferiority was established for the SST $\leq$ 30 μg/hour compared with IV MS. Additionally, the SST $\leq$ 30 μg/hour showed superiority to IV MS based on the PGA24 and HPGA24 responses. In the first 24 hours after start of treatment, the SST $\leq$ 30 μg/hour produced significantly better pain responses than IV MS, including more rapid onset of pain control. While this study was conducted in post-operative patients, the IV MS group self-administered a median dose of 10 mg over the first 3 hours, which is not dissimilar to the total amount of IV MS bolus doses administered in an ER setting over this time period. Whereas larger and less frequent boluses of IV MS may slightly shorten the time for morphine to reach the CNS compared to IV MS 1 mg doses administered more frequently with patient-controlled analgesia, the very slow plasma:CNS equilibration time of morphine (2.8 hours) compared to sufentanil (6 minutes) results in an advantage for sufentanil with respect to onset of analgesia. Therefore, the efficacy results (original IAP309 study and post hoc analysis) for SST versus IV MS support the sought moderate to severe pain patient population who may currently be treated with bolus IV MS injections for their pain.

2.5.2. Discussion on clinical efficacy

A three-arm, active controlled study was not performed. This would be generally required to demonstrate the magnitude of the clinical effect of the test treatment in comparison with the known effective treatments for the pain models being studied. In this case, however, performing such a study was not considered feasible due to the specific device needed for delivery of the sublingual tablet. Blinding the study cannot be made in such case as the test product is applied by a specific device and the reference product can be administered intravenously or epidurally. There is no reference product that would be indistinguishable from SST NanoTab 30µg tablet.

Formal dose-response studies have not been performed. The Applicant has submitted one phase 2 study, SAP202, which was also intended to be a pivotal efficacy study. In addition to the studies conducted by SST NanoTab sublingual sufentanil tablet administered by a health care professional the Applicant has submitted full reports of the studies already assessed in the marketing authorization process of Zalviso. These studies include two dose-finding studies, ARX-C-001 (sufentanil doses of 5 µg, 10 µg and 15 µg in elective unilateral knee arthroplasty) and ARX-C-005 (sufentanil doses of 10 µg 15 µg in open abdominal surgery).

Two controlled, randomized, double-blind studies have been conducted. SAP 202 study was originally a dose finding phase 2 study. However, the Applicant has not performed phase 3 study to prove the efficacy of 30µg sufentanil in somatic pain, therefore this study serves as an efficacy study of somatic pain. As the statistical power is sufficient, this approach has been accepted.

In study 202, the study population was representative to the whole human population in terms of age and gender. The total ITT population number is 100 disposed in three treatment arms (placebo, 20µg sufentanil, 30µg sufentanil). 4 percent (e.g. 4 patients in this case) were at least 65 years old. This small number of elderly patients does not make the subpopulation statistical analysis feasible and the Applicant has not performed such analysis either. The inclusion and exclusion criteria are appropriate.

The treatment assignment was appropriate. 20 patients received placebo, 40 patients received 20µg, 40 patients received 30µg sufentanil. The use of rescue medication seems sufficient considering the somatic postoperative pain that may respond well to a combination of weak opioids and acetaminophen.

The primary and secondary efficacy endpoints were appropriate and generally accepted in pain studies. The total observation time of 12 hours was sufficient. Postoperative pain is declining by nature as the wound is healing there is no necessity to measure analgesic effects longer after this type of surgery.

The sample size was sufficient in to detect statistically significant differences between groups.

The study is balanced in terms of gender, however, white population was overrepresented. Since opioids are generally efficient analgesics in the whole human population the race imbalance most likely does not bias the results.

Study 301 study was designed and conducted as a phase 3 double-blind randomized, controlled trial to test 30µg sublingual sufentanil for postoperative visceral pain.

The study population and treatment was appropriate: A total of 163 patients (109 sufentanil, 54 placebo) were enrolled and randomized in this study; two patients (both in the sufentanil group) did not receive study drug, leaving 161 patients who received study drug and were included in the ITT and safety populations. The use of rescue medication (1 mg IV morphine) was sufficient considering the visceral postoperative pain.

The amendments of the protocol are adequate, all the additions and clarifications as stated in Study Protocols are reasonable. Protocol deviations were handled appropriately.

The study was imbalanced in terms of gender and white population is overrepresented. There were approximately double number of women than men. The relatively low number of males might result in ambiguous evaluation of efficacy in this subgroup. There were only two patients over 65 years of age. Since opioids are generally efficient analgesics in the whole human population the race imbalance most likely does not bias the results but subgroup analysis by gender might not be informative.

In both double-blind controlled studies three statistical issues have emerged.

Two of them were related to applied imputation method. The Applicant provided additional sensitivity analysis which proved that the missing data imputation method had a small effect on the primary endpoints. The impact of imputation method on the results was small because only small percentage of the data had to be imputed. Even using a not realistic and extremely conservative approach gave clinically significant though statistically borderline results.

A special case of missing data was data of patients who used any rescue medication. When this happened, the last observed pain intensity before using each dose of rescue medication was carried throughout a follow-up 1-hour time interval. This 1-hour time interval seemed short, and the statistical analysis was requested assuming that the rescue medication had longer effect. It has been clarified that the dose of morphine was lower than usual, and the majority imputed period length was much longer than one hour due to study design. The Applicant also pointed out that longer missing data period would be anti-conservative measure, i.e., would be biased toward the active treatment arm. These points were considered valid arguments and it was accepted that further statistical analysis is not needed.

Concern was raised that in study SAP202 the mean percentage of observed pain data that was collected prior to the use of rescue medication was higher in the sufentanil groups than in the placebo group (50.97% for SST 30 mg vs 32.02% for SST 20 mg vs 23.72% for placebo; $p < 0.001$ for the overall comparison among groups). The Applicant clarified that this difference was due to the specific features of the study design. The delay in the request of rescue medication was the proof of the clinical efficiency. However, the perceived pain prior the rescue medication is a parameter which cannot be easily interpret. This scenario adequate for a Phase 2 study but does not reflect the intended use. Because of that, the average pain until the rescue medication is a parameter which has no clinical relevance.

In both studies, the primary efficacy endpoint showed the superiority of 30µg sufentanil administered sublingually by a health care professional for postoperative somatic and visceral pain to placebo.

In both studies the secondary endpoint analysis clearly supports the conclusion drawn from the primary efficacy endpoint. The analgesic effect can already be seen within the first hour. Sufentanil in 30µg is superior to placebo in the analgesic effect against somatic and visceral postoperative pain.

The most surprising data in study SAP202 in terms of withdrawal is the highest percentage inefficiency (7.5%) in the 30µg sufentanil group (3 patients). In study SAP301 18 patients terminated the study within the first 24 hours, 5 from the sufentanil group an 13 from the placebo group. The most common reason in the placebo group was the lack of efficiency (10 patients). Lack of efficacy in the sufentanil group was the reason of withdrawal in 4 patients. More than 50% of the patients did not enter the second period (24 hours – 36 hours) mostly due to discharge and recovery. 21 and 9 patients entered the 36 hour -48 hour period from the sufentanil and placebo groups, respectively. All patients

recovered by the end of the study period. During the whole study period 6 and 12 withdrawals occurred due to lack of efficacy from the sufentanil and placebo groups, respectively.

The Applicant was requested to compare the plasma levels of sufentanil in patients who were withdrawn due to lack of efficacy (30µg sufentanil groups in both studies) with the ITT population plasma concentrations especially around the time-points of the administration of rescue medication and summarize the pain intensity data after the rescue medication to see whether the rescue medication was effective or not. These data was intended to clarify whether these patients did not respond due to insufficient plasma level of sufentanil or would have required even higher dose of sufentanil.

In SAP202 sufentanil concentration data were available at 1 and 4-hour time points for all three patients. The Applicant proposes three possible reasons of lack of efficacy: 2 of 3 patients had lower plasma levels than the average sufentanil concentration but data do not indicate swallowing the pill instead of keeping it in the mouth. Therefore, it can be considered as an individual difference and lower sensitivity to opioids. The third patient had 53% concentration of the average sufentanil plasma level by the 4th hour but strangely the patient did not require frequent administration, the interdosing average interval was more than two hours (1 hour dosing interval was allowed as maximum). The lack of efficacy of the rescue medication (Vicodin = hydrocodone) further indicates low opioid induced analgesic response.

In SAP301 only one patient had no measurable sufentanil concentration that indicates swallowing, the other 6 patients had no significantly lower sufentanil exposure. Again, the reason of lack of efficacy might be again a different individual sensitivity or, - considering the less than maximal possibilities of dosing - even patients' misunderstanding of the way of using sufentanil.

As these patients' pain intensity scores did not change after taking sufentanil or rescue medication the Applicant's argumentation about the need for multimodal analgesia can also be considered. One question was not answered by the Applicant, the possible need for even higher doses of sufentanil but this cannot be answered from the data of the studies.

Generally patients in the 30µg sufentanil groups required less rescue medication although the percentage was high in SAP202. Nevertheless, the time to the first rescue medication was significantly longer in both studies.

The Applicant has provided a discussion about the clinical relevance of sublingually administered 30µg sufentanil on the patient's request with a maximum hourly frequency in postoperative settings. The Applicant was asked to provide a responder analysis as it could answer the clinical significance of the proposed analgesic medication.

The definition of the clinically meaningful response was based on literature data. The Applicant's approach that instead of the absolute numbers the percentage difference was used is acceptable.

For each trial diagrams plotting percentual pain intensity difference against the proportion of patients receiving the respective percentual difference were provided. Assuming that a 50% reduction could be regarded as a relevant effect in the acute pain setting, this was reached in the 12 h interval by less than 20% in SAP 202, approximately 50% in SAP301 and more than 60% in SAP303 patients. In the 1h interval 50% pain reduction was reached by approximately 50% of the patients in SAP 301. The Applicant has provided a table summarizing the percentage of responders at 1 and 12 hour time points in three and at 1 hour time in one (emergency setting) studies.

Table 2 Responder Analysis at 1 and 12 Hours Based on Mean Baseline Pain Intensity Scores

Study (Clinically Relevant % Decrease in Pain Intensity)	Proportion of Responders at 1 Hour		Proportion of Responders at 12 Hours	
Postoperative	**Active**	**Placebo**	**Active**	**Placebo**
SAP202 (20%)	73%	25%	43%	30%
SAP301 (23%)	58%	20%	76%	57%
SAP303 (21%)	62%	n/a	87%	n/a
Emergency				
SAP302 (22%)	65%	n/a	n/a	n/a

The Applicant was also asked to justify the rationale for selecting a dosing interval of 1h between the 30μg SST doses. The choice of 30μg sufentanil given hourly as maximum frequency has been based on the Zalviso studies where because of the 20 minutes lock-time and the 15μg sufentanil single dose the maximum hourly dose of sufentanil could be 45μg. The median utilization in the Zalviso studies was 30μg sufentanil in an hour. The Applicant's choice of dose was acceptable.

Study 302 was considered to be supportive for efficacy of sufentanil 30 μg sublingual tablet. Pain intensity decreased as early as 15 minutes following administration of treatment and pain relief was maintained 2 hours post-dose. Fast onset of effect is of paramount importance in emergency setting, however, the benefit of a sublingual tablet is not straightforward as most patients in emergency rooms must have i.v. canules, thus, i.v. administration of painkillers can also provide rapid onset of analgesic effect. Otherwise, due to small sample size, heterogeneity of population, open-label design and lack of comparator, this study provide limited additional evidence to the efficacy evaluation.

Similarly, study 303 is also supportive for efficacy of sufentanil 30 μg sublingual tablet. In this case patients after abdominal or orthopaedic surgery received 30μg sufentanil and SPID12 was the primary efficacy endpoint. In this case the indication fits the intended indication of SST Nanotab 30μg pill. The primary efficacy endpoint was numerically higher in patients after abdominal surgery but the difference seems insignificant. Pain intensity decreased as early as 15 minutes or 30 minutes following administration of treatment and pain relief continued to improve over 2 hours and the improvements were maintained throughout the 12-hour study period. Acknowledging that sublingual sufentanil can provide an as rapid as 15 minutes onset after administration the benefit is not unequivocal. In the postoperative period patients must have an iv. canule and i.v. administration of painkillers can provide an immediate onset of analgesic effect. Since both an intravenous analgesic both sufentanil sublingual pill is given by a health care professional even the benefit of the patient controlled analgesia is missing as an advantage. Overall, due to the open-label design and lack of comparator, this study provided limited additional evidence to the efficacy evaluation.

Study IAP309 was a multicentre, randomized, open-label, parallel-group trial designed to compare the Zalviso System (SST 15 μg) to IV MS for at least 48 hours, and up to 72 hours if needed, in patients 18 years and older who had undergone a major open abdominal surgery (including laparoscopic-assisted open abdominal procedures) or orthopedic (total knee or hip replacement) under general or spinal anesthesia that did not include intrathecal opioids during the operation.

Reanalysis of study IAP309 compared the efficacy of the SST 15 μg to IV MS, by comparing the IV MS group to only those SST 15 μg patients who dosed 30 μg or less (≤ 2 doses of SST 15 μg) per hour.

During scientific advice discussions with European Health Authorities regarding the SST 30 μg, the Health Authorities recommended re-analyzing the efficacy data.

The primary objective of the re-analysis was to evaluate whether the SST 15 µg was non-inferior to IV MS in the management of moderate-to-severe post-operative pain after major abdominal or orthopedic surgery as assessed by the PGA at 24 hours using a 4-point categorical scale with success defined as a report of “good” or “excellent” on the PGA24.

This post-hoc analysis of the Zalviso study IAP309 was suggested by a scientific advice. Indeed, comparing paiteints who received less or equal than 2 of 15µg sufentanil sublingual pills in the first hour of the postoperative period with iv. morphine given by the patients with an infusion pump is reasonable. The results showed non-inferiority ($p<0.001$) and superiority ($p=0.002$) of sublingual sufentanil to iv. morphine in the primary endpoint (Patient Global Assessment, PGA). Secondary endpoints also indicated non-inferiority of sublingual sufentanil to iv. morphine. One of the most interesting results of the analysis was the patients’ judgment about the onset of action that was faster in the sufentanil group. That was surprising since iv administration should theoretically provide an immediate response. It must be noted though that the study was open-label which was unavoidable as the different ways of administration would have made blinding impossible. Therefore the patients were aware of the study drug and the new non-invasive way of giving an analgesic might have resulted in higher expectations. The way of the treatment of postoperative pain was also different as in study IAP309 PCA (patient controlled analgesia) was applied. Overall, the analysis can be considered supportive for the current application.

The anaesthesia methods and allowed postoperative medications were stricter in the controlled studies than in the open label ones. In SAP202 (bunionectomy) besides iv propofol or midazolam for sedation and iv. fentanyl as an analgesic the main anaesthetic procedure was a local metatarsal blockade. This in fact influenced the analgesic efficiency of sufentanil in the first three-four hours as an increase in the pain intensity could be observed between 4 to 7 hours postoperatively. It possibly reduced the need for sufentanil in the first 4 hours of the study. The same problem might have occurred in the open label uncontrolled SAP303 study in patients with bunionectomy. In the study SAP301 general anaesthetic procedures were applied in all patients and no additional analgesics were allowed after surgery but the study drug. Therefore, the efficiency of sufentanil was not altered by concomitant medication. Since patients could receive their first sufentanil dose postoperatively when the reported pain score reached 4 they were standardized and the general anaesthetic procedure obviously did not influence the analgesic effect of sufentanil. The Applicant’s response is clear and acceptable. In the study SAP303 multimodal analgesia was allowed postoperatively but the evaluation of the impact on sufetanil effect is highly limited due to the open label uncontrolled design of the study.

Another concern was raised as surgical patients need to sleep at night and an administration of the drug every hour will obstruct this. Postoperative pain management will often change from iv to oral medication with longer duration of action within the first hours postoperatively or a mixture of oral and iv administration.

In order to assess the true effect of SST 30 ug/hour, the Applicant was asked to provide data regarding peroperative medication of the mentioned drugs. In the controlled efficacy studies no other analgesic except rescue medication was used. Antiemetics were used when needed, dexamethasone was not administered. In study SAP303 real-life settings were allowed but the effect of other analgesics cannot be evaluated as there was no comparison in that study

2.5.3. Conclusions on clinical efficacy

In the pivotal trials 30µg SST demonstrated superiority over placebo for primary endpoint and key secondary endpoints. Efficacy was rapid in onset and durable over time. Observed pain responses were clinically meaningful. The data obtained from the clinical development of Zalviso can be accepted as supportive for Dzuveo MAA evaluation.

2.5.4. Clinical safety

Sufentanil has been available in the EU since 1978 and its safety profile is well characterised. Sufenta Forte solution for injection 0.05 mg/mL was approved in 1982 in Netherland for IV anesthetic use. The dosage and route of administration of Sufenta differs from that of the SST. Sufenta is administered IV at high doses for anesthesia and epidurally in conjunction with bupivacaine for analgesia.

In 2014, Grunenthal (AcelRx licensed Zalviso to Grunenthal in the EU) presented Zalviso, a 15 µg sufentanil tablet combined with a PCA dosing system, which allowed patients to self-administer 15 µg sufentanil tablets sublingually after major abdominal/orthopaedic surgery. In Zalviso Phase-3 clinical studies, there were numerous patients, administering sufentanil doses very similar to that in the current application (i.e. 15 µg over 20-25 minutes). Applicant was intended to use safety data obtained from these patients to support the present application. According to the scientific advice sought from FDA, use of safety data obtained from Zalviso patients taking 15 µg of sufentanil over every 20-25 minutes was considered acceptable only if cmax values were justified to be similar enough for the two different dosage regimens and tablet strengths. According to Applicant's data obtained from SAP101 PK study this was the case.

Key safety characteristics of reference product and Zalviso

The most serious adverse reaction of sufentanil is respiratory depression, with dose-related severity and potentially leading to apnoea and respiratory arrest. Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. Respiratory depression caused by sufentanil can be reversed by opioid antagonists. Repeat antagonist administration may be required as the duration of respiratory depression may last longer than the duration of the effect of the antagonist. In Zalviso clinical studies, nausea and vomiting were the most frequently reported adverse reactions (≥1/10 frequency).

Furthermore, common adverse drug reactions identified either from Zalviso clinical studies or from post-marketing experience of other sufentanil-containing medicinal products were confusional state, dizziness, headache, sedation, bradycardia, hypotonia, hypertonia, constipation, dyspepsia, pruritus, involuntary muscle spasms and urinary retention.

Patient exposure

Table Overall sufentanil sublingual tablet exposure

Study Identifier	Phase	Population Studied/ Study Type	Total Subjects Exposed to SST 30 or 15 mcg Active Dose[a]
ARX-04 Studies (SST 30 mcg)			
Phase 3 Studies			
SAP301	3	Post-surgical (abdominal surgery)/RDBPC	107
SAP302	3	Patients presenting to ER with acute moderate to severe pain/OL	76
SAP303	3	Postsurgical/OL	140
		Total in Phase 3 Studies	323
Phase 2 Studies			
SAP202	2	Post-bunionectomy/RDBPC	40
		Total in Phase 2 Studies	40
Phase 1 Studies			
SAP101	1	Healthy adults[b]/PK OL	40
		Total in Phase 1 Studies	40
		Total in ARX-04 Studies	**403**
Supporting Studies (SST 15 mcg doses equivalent to SST 30 mcg[a])			
Phase 3 Studies			
IAP310	3	Post-surgical (abdominal surgery) inpatients/RDBPC	51
IAP311	3	Post-surgical (major orthopedic surgery) inpatients/RDBPC	142
IAP309	3	Post-surgical (abdominal or orthopedic) inpatients/OL, active comparator (IV PCA morphine)	94
		Total in Phase 3 Studies	287
Phase 2 Studies			
ARX-C-001	2	Postoperative inpatients/RDBPC	12
ARX-C-005	2	Postoperative inpatients/RDBPC	6
ARX-C-004	2	Postoperative inpatients/OL	18
		Total in Phase 2 Studies	36
		Total in Supporting Studies	**323**
OVERALL TOTAL		**Healthy subjects and patients exposed to SST 30 mcg**	**403[c]**
		Patients exposed to SST 30 mcg	**363[d]**
		Patients exposed to SST 30 mcg or equivalent SST 15 mcg doses	**686[a]**

Abbreviations: ER = emergency room; IV = intravenous; OL = open-label; PC = placebo-controlled; PCA = patient-controlled analgesia; PK = pharmacokinetic; RDBPC = randomized, double-blind, placebo-controlled.

[a] This includes subjects or patients exposed to SST 30 µg or equivalent doses of SST 15 µg (ie, patients who received 2 SST 15 µg dosed within 20-25 minutes of each other in the first hour of dosing). Inclusion of SST 15 µg patients in analyses with SST 30 µg (ARX-04) is based on the establishment of bioequivalence of 1 SST 30 µg with 2 SST 15 µg dosed within 20 minutes of each other and PK modeling.

[b] Healthy adults in this study were naltrexone-blocked.

[c] All SST 30 µg exposure, including subjects in the ARX-04 Phase 1 study who were naltrexone-blocked and patients in Phase 2 and 3 studies.

[d] n = Patients exposed to SST 30 µg in Phase 2 and Phase 3 studies.

The total pooled patient database (All Patient Pool) includes 363 patients who received SST 30 mcg and 323 who received equivalent doses of SST 15 mcg (2 SST 15 mcg dosed within 20 to 25 minutes of each other). A total of 686 patients received SST 30 mcg or equivalent doses of SST 15 mcg for any length of time.

Across all integrated studies, SST 30 mcg was received by:

- 212 patients for ≥ 6 hours
- 94 patients for ≥ 12 hours
- 25 patients for ≥ 24 hours
- 1 patient for ≥ 48 hours

Equivalent doses of SST 15 mcg were received by:

- 292 patients for ≥ 6 hours
- 255 patients for ≥ 12 hours
- 226 patients for ≥ 24 hours
- 101 patients for ≥ 48 hours

Pooling strategy

The pooled analyses include data collected from studies conducted under the ARX-04 program and from a selected patient population that was included in the Zalviso 15 µg marketing application approved in April 2016 (EU/1/15/1042). The selected Zalviso population includes patients who self-administered Zalviso (SST 15 µg) or placebo with the second dose administered within 20 to 25 minutes after the first dose. From the ARX-04 and Zalviso studies, results for the following pooled groups are presented:

- Pool 1, All Patient Pool (N = 904) Analysis includes 5 treatment groups: SST 15 µg, SST 20 µg, SST 30 µg, ARX-04 placebo, and Zalviso placebo
- Pool 2, All ARX-04 Patient Pool (N = 437). Analysis includes 2 treatment groups: SST 30 µg and ARX-04 placebo.
- Pool 3, ARX-04 Placebo-controlled Patient Pool (N = 221). Analysis includes 2 treatment groups: SST 30 µg and ARX-04 placebo
- Pool 4, Zalviso Placebo-controlled Patient Pool (N = 315). Analysis includes 2 treatment groups: SST 15 µg and Zalviso placebo.
- Pool 5, Combined Placebo-controlled, All Patients Pool (N = 536). Analysis includes 2 treatment groups: combined SST (15 µg and 30 µg) and combined placebo (ARX-04 and Zalviso placebo)
- Pool 6, Open-label Study Pool (N = 328). Analysis includes 2 treatment groups: SST 15 µg and SST 30 µg.

An additional comparative analysis between Sufentanil 30 µg patients and the above mentioned subset of Zalviso patient (N = 323) was also carried out. Within these patients, there was a subset who self-administered a third dose of the SST 15 µg in the first hour of treatment (ie, 45 µg/hour), which exceeds the dose of sufentanil received from the maximum SST 30 µg dosage of 1 tablet per hour. Safety data for this subset who received 3 doses and for those who received 2 doses are presented

and analysis has been performed for the two different 2 treatment groups i.e. 2 × SST 15 µg and 3 × SST 15 µg.

Table Patient study pools for safety analyses

Studies	ARX-04 Studies (SST 30 mcg)				Zalviso Studies (Selected SST 15 mcg Population[a])					
	Phase 2	Phase 3			Phase 2			Phase 3		
	SAP202	SAP301	SAP302	SAP303	ARX-C001	ARX-C004	ARX-C005	IAP309	IAP310	IAP311
N (SST 30 mcg or selected SST 15 mcg; patients who received 30-45 mcg/hour)	40	107	76	140	12	18	6	94	51	142
N (placebo)	20	54			15		8		27	54
1. All Patient Pool	X	X	X	X	X	X	X	X	X	X
2. All ARX-04 Patient Pool	X	X	X	X						
3. ARX-04 Placebo-controlled Patient Pool	X	X								
4. Zalviso Placebo-controlled Patient Pool					X		X		X	X
5. Combined Placebo-controlled, All Patients Pool	X	X			X		X		X	X
6. Open-label Study Pool			X	X		X		X		
Zalviso Dose Comparison Analysis					X	X	X	X	X	X

This report contains a detailed discussion of safety data for Pools 2, 3 and 5.

Demographic and baseline characteristics

Pool 3 (ARX-04 placebo-controlled patient pool)

In Pool 3, most of demographic and baseline characteristics were similar for sufentanil and placebo groups. However, a greater number of patients with ASA Class I and Class III was randomised to placebo. BMI distribution also was different for sufentanil and placebo groups: there were more patients with BMI<30 and BMI >40 in the sufentanil groups. Maximum BMI in Pool 3 clinical studies was much higher (53.5) in the sufentanil group than in the placebo group (39.2)

Pool-2 (All ARX-04 Patient Pool)

Across *all pooled studies* of SST 30 µg (All ARX-04 Patient Pool, Pool 2), compared with the subset of placebo-controlled studies of SST 30 µg, the patients were generally older (mean age 46.7 vs. 41.7 years), with a lower ASA class (50.7% vs. 63.9% were ASA Class I). These differences are largely

attributed to the inclusion criteria of the different studies, particularly the open-label study SAP303, which enrolled patients 40 years or older. In addition, the placebo-controlled studies enrolled patients who underwent orthopaedic or abdominal surgery, (i.e. the indication in these studies was moderate to severe post-operative acute pain) while the open-label studies enrolled patients who underwent any type of surgery (SAP301, 303 and 202) or who had pain due to trauma or injury (SAP302). Proportion of female patients in sufentanil groups was also higher for ARX 04 placebo-controlled pool (Pool 3, 63.3%) than for All ARX-04 pool (Pool 2, 54.5%). There were also a lower proportion of Hispanic patients (22.3%) in Pool 2 than in Pool 3 (32.0%). Caucasian patients occurred with frequency of 52.9% in sufentanil groups in Pool 2 and 42.2% in Pool 3.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

In Pool 5, most of demographic and baseline characteristics were similar for sufentanil and placebo groups. There were more ASA Class I and Class III patients in the placebo groups, whereas more ASA Class II patients were randomised to sufentanil groups in placebo-controlled Sufentanil 30 SST and Zalviso studies. More patients with BMI between 30 and 40 were randomised to placebo groups, and proportion of patients with BMI>40 is higher in sufentanil groups. Maximum BMI experienced in the studies is also much higher in sufentanil group.

Rescue therapy

Rescue therapy IV morphine was used in SST 30 µg studies SAP 301 and SAP 303, IV morphine or oral oxycodone were used in study SAP 302 and oral hydrocodone-acetaminophen combination was used in study SAP202. Proportion of patients not requiring rescue medication varied from 30.0% (SAP202) to 85.7% (SAP303, total).

Adverse events

Table 2.7.4:15 **Most common (occurring in at least 1% of patients in any treatment group) adverse events during the 24-hour period after the 1st dose: patients enrolled in ARX-04 placebo-controlled studies SAP202 and SAP301 (ARX-04 Placebo-controlled Patient Pool)**

	Treatment Group		
	Sufentanil 30 mcg	ARX-04 Placebo	Treatment p-value[a]
Number of Patients Enrolled in the Study	147	74	
Number (%) of Patients Who Received Treatment	147 (100%)	74 (100%)	
Number (%) of Patients Without Any Adverse Event	55 (37.4%)	38 (51.4%)	
Number (%) of Patients With at Least One Adverse Event	92 (62.6%)	36 (48.6%)	0.060
Number (%) of Patients Who Reported Adverse Events by System Organ Class			
CARDIAC DISORDERS	4 (2.7%)	0	NS
Tachycardia	3 (2.0%)	0	NS
GASTROINTESTINAL DISORDERS	64 (43.5%)	19 (25.7%)	0.012
Nausea	60 (40.8%)	16 (21.6%)	0.005
Vomiting	19 (12.9%)	1 (1.4%)	0.005
Flatulence	4 (2.7%)	4 (5.4%)	NS
Dry mouth	3 (2.0%)	0	NS
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (2.0%)	3 (4.1%)	NS
Procedural nausea	3 (2.0%)	3 (4.1%)	NS
NERVOUS SYSTEM DISORDERS	41 (27.9%)	14 (18.9%)	NS
Headache	21 (14.3%)	10 (13.5%)	NS
Dizziness	14 (9.5%)	3 (4.1%)	NS
Somnolence	11 (7.5%)	2 (2.7%)	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (5.4%)	2 (2.7%)	NS
Pruritus	6 (4.1%)	2 (2.7%)	NS
VASCULAR DISORDERS	8 (5.4%)	3 (4.1%)	NS
Hypotension	5 (3.4%)	1 (1.4%)	NS
Hypertension	2 (1.4%)	1 (1.4%)	NS

Abbreviation: NS = not significant.
Note: Most frequent adverse events are those events that were reported by at least 1% of all patients. Adverse event mapping was based on the MedDRA Version 11.0 thesaurus. A patient may be reported in more than 1 category. Adverse events occurring while patients are on study medication during the study treatment period or within 12 hours after the discontinuation of study medication are included in this data analysis up to 24 hours after first dose of study drug.
[a] The p-values for the comparison between 2 treatment groups are based on a 2-sided Fisher's exact test and presented if they are less than 0.1; NS = $p \geq 0.10$ (statistical significance was defined as $p < 0.05$; therefore, not statistically significant p values between 0.05 and 0.10 are presented in the table).
Source: ISS Table 17

Adverse event mapping was based on the MedDRA Version 11.0 thesaurus. A patient may be reported in more than 1 category. Adverse events occurring while patients are on study medication during the study treatment period or within 12 hours after the discontinuation of study medication are included in this data analysis up to 24 hours after first dose of study drug. The p-values for the comparison between 2 treatment groups are based on a 2-sided Fisher's exact test and presented if they are less than 0.1; statistical significance was defined as $p < 0.05$; therefore, not statistically significant p values between 0.05 and 0.10 are presented in the table. If $p \geq 0.1$, difference between the two treatment groups was considered as non-significant and was signed as NS in AE tables.

In Pool 5, patients who received either: 1) SST 30 µg or 2) 2 SST 15 µg dosed within 20-25 minutes of each other in the first hour of dosing were included. Inclusion of these patients in pooled analyses with SST 30 µg (ARX-04) is based on the establishment of bioequivalence of 1 SST 30 µg with 2 SST 15 µg dosed within 20 minutes of each other and PK modeling. All patients in this pool received 30 to 45 µg of sufentanil in 1 hour.

Common adverse events

Pool 3

In Pool 3, AEs experienced by > 5% of patients receiving the SST 30 µg were nausea (40.8%), headache (14.3%), vomiting (12.9%), dizziness (9.5%), and somnolence (7.5%). Results for this pool are similar to results for the Pool 5 discussed below and consistent with those expected of opioid treatment.

Based on Fisher's exact test comparison, 2 common AEs occurred statistically significantly more frequently ($p < 0.05$) in the SST 30 µg group compared with the placebo group: Nausea (40.8% vs. 21.6%, $p = 0.005$) Vomiting (12.9% vs. 1.4%, $p = 0.005$) Incidence of AEs dizziness and somnolence were both at least twice in the active treatment versus placebo.

Pool 2

In Pool 2, common AEs were generally consistent with those observed in the placebo-controlled studies of SST 30 µg, although the proportion of patients with AEs was lower across all studies than in the pooled placebo-controlled studies. For patients receiving SST 30 µg, 44.1% in all studies and 62.6% in placebo-controlled studies experienced AEs. In the SST 30 µg group, AEs experienced by > 5% of patients were nausea (28.9%), headache (8.0%), vomiting (6.3%), and dizziness (5.8%).

Pool 5

In the SST group, AEs experienced by > 5% of patients were nausea (43.9%), vomiting (11.7%), headache (9.2%), dizziness (6.7%), and pruritus (5.3%). Overall, more patients in the SST group (69.0%) experienced AEs than patients in the placebo group (52.8%), and the most common AEs are consistent with those expected of opioid treatment given in a postsurgical setting.

Common opioid-related AEs of oxygen saturation decreased, dizziness, somnolence, and pruritus were all at least twice the frequency of occurrence in the active treatment versus placebo, as were the AEs of anemia, tachycardia, and hyponatremia, which are most likely attributed to the postoperative setting. Specifically, the 7 patients with an AE of oxygen saturation decreased were all enrolled in the SST 15 µg studies (IAP310 and IAP311), with 6 experiencing mild oxygen saturation decreased and continuing in the study and 1 experiencing severe oxygen saturation decreased and withdrawing from the study (study IAP311).

Comparison with Zalviso patient pools

Results were consistent across pooled patient populations, as the most common AEs in all pooled groups were generally consistent with those expected of opioid treatment. However, AEs were more

common in patients receiving SST 15 µg (80.8% of patients experienced AEs) than in patients receiving SST 30 µg (44.6% of patients experienced AEs). This may be attributed to the fact that a generally younger population received the SST 30 µg, and over half of the patients treated with SST 15 µg received a third dose in the first hour of treatment, which exceeds the dose of sufentanil received from the maximum SST 30 µg dosage of 1 tablet per hour (see ISS Section 10 for additional discussion, including comparison of AEs between patients who received 2 or 3 doses of SST 15 µg).

Pool 5 consists on safety results of Zalviso placebo-controlled clinical studies as well those obtained from Sufentanil SST 30 µg placebo-controlled studies. However, incidences of common AEs did not increase in a similar manner than in Zalviso patients taking 30-45 µg of sufentanil during one hour.

Related AEs

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

AEs considered related to study treatment based on investigator-determined judgments in placebo-controlled studies of the SST 30 µg (Pool 3) were experienced by 78 patients (53.1%) in the SST 30 µg group and 23 patients (31.1%) in the placebo group ($p = 0.003$). In the SST group, the most common treatment-related AEs (experienced by ≥ 2% of patients) were nausea (36.7%), vomiting (11.6%), dizziness (9.5%), headache (8.2%), somnolence (6.8%), hypotension (3.4%), pruritus (2.7%), and procedural nausea (2.0%). Results for this pool are similar to results for the Combined Placebo-controlled, All Patients Pool discussed below.

Pool 2 (All ARX-04 Patient Pool)

Across all pooled studies of SST 30 µg,(Pool 5) AEs considered related to study treatment were generally consistent with those observed in the placebo-controlled studies of SST 30 µg, although the proportion of patients with treatment-related AEs was lower across all studies than in the pooled placebo-controlled studies of SST 30 µg. For patients receiving SST 30 µg, 36.9% in all studies and 53.1% in placebo-controlled studies experienced AEs. In the SST group, the most common treatment-related AEs (experienced by ≥ 2% of patients) were nausea (26.7%) and vomiting (5.8%).

Pool 5 (Combined Placebo-controlled, All Patients Pool)

AEs considered related to study treatment based on investigator-determined judgments in the combined placebo-controlled studies of SST 30 µg and SST 15 were experienced by 179 patients (50.0%) in the SST group and 55 patients (30.9%) in the placebo group ($p < 0.001$). In the SST group, the most common treatment-related AEs (experienced by ≥ 2% of patients) were consistent with expected AEs of opioid treatment and included nausea (33.2%), vomiting (10.3%), dizziness (6.1%), headache (4.7%), pruritus (3.9%), somnolence (3.6%), and hypotension (2.8%).

Comparison with Zalviso patient pools

Results were consistent across pooled patient populations, as the treatment-related AEs in all pooled groups were generally consistent with those expected of opioid treatment and the treatment settings. However, treatment-related AEs were more common in patients receiving SST 15 µg (55.1% of patients experienced treatment-related AEs) than in patients receiving SST 30 µg (37.2% of patients experienced treatment-related AEs). This may be attributed to the fact that a generally younger

population received the SST 30 µg, and over half of the patients treated with SST 15 µg received a third dose in the first hour of treatment, which exceeds the dose of sufentanil received from the maximum SST 30 µg dosage of 1 tablet per hour (see ISS Section 10 for additional discussion, including comparison of AEs between patients who received 2 or 3 doses of SST 15 µg).

AEs by severity

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

In placebo-controlled studies of the SST 30 µg,(Pool 3) most AEs were judged to be mild in severity. In the SST 30 µg group, moderate AEs experienced by ≥ 2% of patients were nausea (25.2%), headache (4.8%), vomiting (4.8%), flatulence (2.7%), dizziness (2.0%), and somnolence (2.0%). In the placebo group, moderate AEs experienced by ≥ 2% of patients were nausea (16.2%), headache (6.8%), flatulence (5.4%), and somnolence (2.7%).

For severe AEs, those experienced by > 1% of patients in the SST 30 µg group were nausea, procedural nausea, and procedural vomiting, each experienced by 2 patients (1.4%). In the placebo group, severe AEs experienced by > 1% of patients were hemiparesis and procedural nausea, each experienced by 1 patient (1.4%).

Pool 2 (All ARX-04 Patient Pool)

The severity of AEs observed in all pooled studies of SST 30 µg (Pool 2) was generally consistent with that observed in the placebo-controlled studies of SST 30 µg. Only 1 severe AE (nausea in 1.1% of patients) and 4 moderate AEs (nausea in 12.7%, headache in 2.5%, vomiting in 1.9%, and flatulence in 1.1%) were experienced by > 1% of patients receiving SST 30 µg in these studies.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

In the combined placebo-controlled studies of SST 30 µg and SST 15 µg (Pool 5), most AEs were judged to be mild in severity. In the SST group, moderate AEs experienced by ≥ 2% of patients were nausea (23.2%), vomiting (4.5%), headache (3.9%), dizziness (2.2%), pruritus (2.0%), and pyrexia (2.0%). In the placebo group, moderate AEs experienced by > 2% of patients were nausea (15.2%), headache (2.8%), and flatulence (2.2%). The moderate and severe AEs reported are consistent with those expected of opioid treatment and the postsurgical setting.

In Pool 5, No severe AEs were experienced by more than 1% of patients in either the SST or placebo group, and the only severe AE experienced by more than 2 patients was nausea, which was reported for 3 patients in the SST group. The severe AE of respiratory rate decreased occurred in an SST 30 µg-treated patient (study SAP202) and the severe AE of oxygen saturation decreased occurred in a SST 15 µg-treated patient (study IAP311; she actually self-administered 14 doses of 15 µg sublingual nanotab during cca 6 hours).

Comparison with Zalviso patient pools

In Zalviso Placebo-controlled Patient Pool (Pool 4) one severe AE (oxygen saturation decreased occurred within the first 24 hours of the study; this severe AE is identical to that in Study IAP311 mentioned above. Other AEs were mild or moderate in severity.

In case of common AEs, related AEs as well as for analysis of AEs in severity incidences of these AE types were lower for All ARX-04 Patient Pool (Pool 2) than for ARX-04 Placebo-controlled Patient Pool (Pool 3) as well as for Combined Placebo-controlled All Patients Pool (Pool 5, this pool contains Zalviso patients taking 30-45 µg of sufentanil during one hour). Same safety results were rather similar for Pool 3 and Pool 5.

AEs of special interest

AEs associated with the use of sufentanil were grouped into 3 areas of special interest for an in-depth analysis: respiratory events, neuropsychiatric events, and gastrointestinal events. Most of the AEs of special interest observed with the SST were mild to moderate and self-limited, and no opioid reversal agents (eg, naloxone) were required for any patient receiving SST 30 µg throughout all Phase 2 or Phase 3 studies.

Analysis of AEs of special interest was presented for Pool 3 and Pool 5 as well as for Zalviso studies pool, but not for Pool 2 (All SST 30 µg patient pool).

Respiratory events

As with any opioid, SST may be associated with respiratory events, particularly in a post-operative setting where patients are recovering from anesthesia or have been administered concomitant CNS depressants, including other opioids during the surgery and during the initial stay in the recovery room. Also, the use of rescue opioids confounds the assessment of AEs.

Vital signs and physical finding linked to respiratory adverse events are also discussed in this section.

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

Most of the respiratory events seen with the SST were mild to moderate and self-limited. Only 1 event in the placebo-controlled studies of the SST 30 µg was considered to be severe and related to study treatment by investigators. Opioid reversal agents (eg, naloxone) were not required for any patient receiving SST 30 µg in these studies. Respiratory AEs by SOC and PT in the SST 30 group were the following: respiratory rate decreased (Investigations) in one patient, and hypoxia (Respiratory Thoracic and Mediastinal Disorders) in one patient.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

Most of the respiratory events seen with SST were mild to moderate and self-limited, with only 2 events considered to be severe and related to study treatment by investigators. The severe AE of respiratory rate decreased occurred in an SST 30 µg-treated patient (study SAP202; patient #1962 narrative) and the severe AE of oxygen saturation decreased occurred in an SST 15 µg-treated patient (study IAP311; patient #8901 narrative). Opioid reversal agents (eg, naloxone) were not required for any patient receiving SST 30 µg throughout all Phase 2 or Phase 3 studies (placebo-controlled or non-controlled studies).

Respiration rate

Across studies of the SST, mean changes from baseline in respiration rate were generally small and not clinically meaningful. However, some respiratory AEs were reported and discussed above.

Oxygen saturation

The lowest oxygen saturation values were identified for each patient and summarized. The mean and median lowest oxygen saturation values, as well as the numbers and percentages of patients with lowest values < and ≥ 95%, < and ≥ 93%, and < 90%, and from 90 to 92% and 93 to 94%, are presented for each pooled group. Note that in order to maintain oxygen saturation at 95%, the study protocols required supplemental oxygen to be available to patients receiving study treatment.

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

In placebo-controlled studies of the SST 30 µg (Pool 3), the mean (SD) lowest oxygen saturation in the SST group was 95.4% (1.4%). This value significantly higher in the placebo group at 96.1% (1.2%) ($p < 0.001$). In addition, higher proportions of patients in the SST group as compared to the placebo group had lowest oxygen saturation values < 95% (17.7% vs 5.4%; $p = 0.012$) and < 93% (5.4% vs. 0%; $p = 0.041$). There were no oxygen saturation values < 90% and no AEs of oxygen saturation decreased in the placebo-controlled studies of SST 30 µg.

Pool 2 (All ARX-04 Patient Pool)

Across all pooled studies of the SST 30 µg,(Pool 5) the mean (SD) lowest oxygen saturation of 95.5% (1.7%) in patients receiving the SST 30 µg was similar to that observed in the placebo-controlled studies (95.4% [1.4%]). Across all pooled studies of SST 30 µg, lowest oxygen saturation values < 95% were observed in 47 patients (12.9%), < 93% were observed in 17 patients (4.7%), and < 90% were observed in 4 patients (1.1%). No patients throughout the ARX-04 Phase 2 or Phase 3 studies required the use of opioid reversal agents (eg, naloxone).

Pool 5 (Combined Placebo-controlled, All Patients Pool)

The mean (SD) lowest oxygen saturation in the SST group was 95.0% (3.4%); this value was significantly higher in the placebo group at 95.7% (1.6%) ($p = 0.001$). In addition, somewhat higher proportions of patients in the SST group as compared to the placebo group had lowest oxygen saturation values < 95% (19.8% vs 15.2%), < 93% (7.8% vs. 3.9%), and < 90 (1.1% vs. 0%). The lowest oxygen saturation value recorded in the SST group was 40%, in a patient receiving SST 15 µg in IAP311. This patient was discontinued due to a severe SAE of oxygen saturation decreased which resolved after treatment with naloxone. The next lowest oxygen saturation value for patients receiving the SST in this patient pool was 83% in a patient receiving SST 15 µg, and the lowest oxygen saturation value for a patient receiving SST 30 µg in these studies was 91%. Overall, 4 patients (1.1%) receiving the SST in placebo-controlled studies had lowest oxygen saturation values < 90%. AEs of oxygen saturation decreased were reported for 7 patients (2.0%) receiving the SST in these studies, of which 1 was considered an SAE and led to discontinuation from the study.

Comparison with Zalviso patient pools

Across all pooled studies, the mean (SD) lowest oxygen saturation values were generally similar for each SST group (94.2% [3.9%] for SST 15 µg, 95.8% [1.0%] for SST 20 µg, and 95.4% [1.8%] for SST 30 µg). It is noted that a generally younger population received the SST 30 µg than received the SST 15 µg, and over half of the patients treated with SST 15 µg received a third dose in the first hour

of treatment, which exceeds the dose of sufentanil received from the maximum SST 30 µg dosage of 1 tablet per hour.

Subgroup analyses

The lowest oxygen saturation values are also presented by age (age < 55 years, 55 to < 65 years, 65 to < 75 years, and ≥ 75 years) and BMI (BMI < 30 kg/m2, BMI ≥ 30 kg/m2 and ≤ 40 kg/m2, and BMI > 40 kg/m2).

Lowest oxygen saturation by age

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

In placebo-controlled studies of the SST 30 µg (Pool 3), there were 192 patients aged < 55 years, 24 aged 55 to < 65 years, and 5 aged 65 to < 75 years. Statistically significant differences in lowest oxygen saturation between the SST and placebo were only observed in the group of patients < 55 years of age, for oxygen saturation < 95% ($p = 0.013$) and mean lowest oxygen saturation ($p < 0.001$). In the conditions and populations under study and in the limited number of patients ≥ 55 years of age in this patient pool, no pattern of additional oxygen desaturation risks was observed in older as compared with younger patients.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

In the combined placebo-controlled studies of SST 30 µg and SST 15 µg, there were 265 patients aged < 55 years, 121 aged 55 to < 65 years, 90 aged 65 to < 75 years, and 60 aged ≥ 75 years. Statistically significant differences in lowest oxygen saturation between the SST and placebo were only observed in the group of patients < 55 years of age, for oxygen saturation < 93% ($p = 0.020$) and < 95% ($p = 0.002$) and mean lowest oxygen saturation ($p < 0.001$).

In patients who received the SST, the mean (SD) lowest oxygen saturation was somewhat lower in patients 65 to < 75 years (94.3% [7.0%]) and ≥ 75 years (94.5% [2.0%]) than in patients < 55 years (95.3% [1.7%]) and 55 to < 65 years (95.2% [1.6%]), but statistically significant differences from placebo were only observed in patients < 55 years. In the conditions and populations under study, no pattern of additional oxygen desaturation risks was observed in older as compared with younger patients.

Comparison with Zalviso patient pools

As for the Combined Placebo-controlled, All Patients Pool and ARX-04 Placebo-controlled Patient Pool discussed above, no pattern of additional oxygen desaturation risks was observed in older as compared with younger patients for Zalviso patient pools.

Lowest oxygen saturation by BMI

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

In placebo-controlled studies of the SST 30 µg (Pool 3), there were 153 patients with a BMI < 30 kg/m^2, 63 with a BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2, and 5 with a BMI > 40 kg/m^2. Statistically significant differences in mean lowest oxygen saturation between the SST 30 µg and placebo were observed in patients with a BMI < 30 kg/m^2 ($p = 0.014$) or 30 to 40 kg/m^2 ($p = 0.005$); none of the 5 patients with a BMI > 40 kg/m^2 received placebo.

A greater proportion of patients receiving the SST with a BMI < 30 kg/m^2 than with a BMI from 30 to 40 kg/m^2 had a lowest oxygen saturation < 93% (5.7% vs. 2.7%) or < 95% (19.0% vs. 13.5%), although the greatest proportion of patients with a lowest oxygen saturation < 93 or 95% (20%) had a BMI > 40 kg/m^2. This differs from the Combined Placebo-controlled, All Patients Pool discussed below, in which a smaller proportion of patients receiving the SST with a BMI < 30 kg/m^2 than with a BMI from 30 to 40 kg/m^2 or > 40 kg/m^2 had a lowest oxygen saturation < 93%.

Overall patient number in Pool 3 was rather low, especially in BMI between 30-40 kg/m^2 and above 40 kg/m^2 categories. Therefore it is hard either to draw any conclusion from the results of oxygen saturation in BMI subgroups or give any explanation of the difference in the results of BMI subgroup analysis for Pool 3 and Pool 5 (see below).

Pool 5 (Combined Placebo-controlled, All Patients Pool)

In the combined placebo-controlled studies of SST 30 µg and SST 15 µg, there were 320 patients with a BMI < 30 kg/m^2, 183 with a BMI ≥30 kg/m^2 and ≤ 40 kg/m^2, and 33 with a BMI > 40 kg/m^2. Statistically significant differences in mean lowest oxygen saturation between the SST and placebo were observed in patients with a BMI < 30 kg/m^2 (p = 0.004) or 30 to 40 kg/m^2 (p = 0.044) but not in patients with a BMI > 40 kg/m^2. Patients with a BMI ≥ 30 kg/m^2 had mean lowest oxygen saturation values lower than those with a BMI < 30 kg/m^2.

Comparing patients receiving the SST in the different BMI groups, the proportion with a lowest oxygen saturation < 93% was lowest in patients with a BMI < 30 kg/m^2 (5.5% had a lowest oxygen saturation < 93%) and higher for patients with a BMI from 30 to 40 kg/m^2 (11.4%) or > 40 kg/m^2 (11.5%). In patients with a BMI 30 to 40 kg/m^2, statistically significantly more patients receiving the SST 30 µg as compared to placebo had a lowest oxygen saturation < 93% (p = 0.042).

Comparison with Zalviso patient pools

In this pool, there were 167 patients with a BMI < 30 kg/m^2, 120 with a BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2, and 28 with a BMI > 40 kg/m^2. No statistically significant differences from placebo were observed in any of the BMI groups. As in the Combined Placebo-controlled, All Patients Pool, the proportion of patients receiving the SST with a lowest oxygen saturation < 93% was lowest in patients with a BMI < 30 kg/m^2 (5.3% had a lowest oxygen saturation < 93%) and higher for patients with a BMI from 30 to 40 kg/m^2 (15.6%) or > 40 kg/m^2 (9.5%).

Neuropsychiatric events

Neuropsychyatric AEs were defined as AE belonging to SOC Nervous System and Psychiatric Disorders. As with any opioid, SST may be associated with neuropsychiatric events, particularly in a postoperative setting where patients are recovering from anaesthesia or have been administered concomitant CNS depressants or medications with psychoactive effects. However, most of the neuropsychiatric events seen with SST were mild to moderate and self-limited, and no neuropsychiatric events of interest were considered to be severe and related to study treatment by investigators.

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

AEs assigned to Nervous system disorders SOC occurred with an overall frequency of 27.9% in SST 30 µg group. Although the difference between SST and placebo groups was assigned as non-significant (NS) for all AEs in Neuropsychyatric AEs group, a trend for more than twofold higher AE frequencies

can be observed in SST 30 µg group, when it is compared to placebo group. Note that NS means that p-value is greater than 0.10 for the given AE frequency.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

Trends of AE frequency difference are similar to that observed in Pool 3, although absolute values of AE frequencies are somewhat lower in Pool 5 than in Pool 3. Frequency values might be more reliable for Pool 5, than for Pool 3 due to the higher patient number in Pool 5.

Gastrointestinal events

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

There were 2 gastrointestinal events of interest in patients receiving the SST 30 µg considered to be severe and related to study treatment by investigators. Statistically significant differences observed between the SST and placebo groups for nausea (40.8% and 21.6%, respectively) and vomiting (12.9% and 1.9%, respectively). P values were 0.005 for both AEs.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

While gastrointestinal events with SST or placebo were common, only 3 gastrointestinal events of interest in patients receiving the SST were considered to be severe and related to study treatment by investigators. Statistically significant differences between the SST and placebo groups were seen for nausea (43.9% and 27.5%, respectively) and vomiting (11.7% and 2.8%, respectively) based on Fisher's exact test comparison. P values were 0.005 for both AEs.

AE and related AE frequencies were similar for GI AEs and related AEs nausea and vomiting for sufentanil groups between Pool 3 and Pool 5. Number of patients experiencing severe GI adverse events were exactly the same for Pool 3 and Pool 5, these were obviously the same patients. Frequency of nausea in placebo groups was somewhat higher for Pool 5 (27.5%) than for Pool 3 (21.6%). Higher patient number in Pool 5 allowed to detect some lower occurrence AEs as constipation, dyspepsia and abdominal distension in sufentanil group; most of them were also considered as treatment-related by the investigator.

Serious adverse event / deaths / other significant events

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

SAEs were followed in placebo-controlled studies of the SST 30 µg (Pool 3) for the 24-hour period after the first dose . During this period, no patients receiving SST 30 µg in the pooled placebo-controlled studies experienced SAEs. In the placebo groups, one patient experienced a SAE of hemiparesis and another patient experienced a SAE of syncope. These were the same two patients mentioned above in SAEs/Pool 2 subsection.

Pool 2 (All ARX-04 Patient Pool)

Across all pooled studies of SST 30 µg, only 1 patient receiving SST 30 µg experienced a SAE (angina pectoris). Two patients from the placebo groups experienced SAEs of hemiparesis and syncope.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

SAEs were followed in the combined placebo-controlled studies of SST 30 µg and SST 15 µg (Pool 5) for the 24-hour period after the first dose. During this period, SAEs were experienced by only 4 patients, including 2 (0.6%) in the SST group and 2 (1.1%) in the placebo group. Two patients experienced SAEs in the SST group within 24 hours of the first dose (1 patient with oxygen saturation decreased, and 1 patient with confusional state, hypoxia, and pulmonary embolism).

There were no deaths in studies of SST 30 µg.

In the Zalviso (SST 15 µg) clinical program, there were 2 deaths, both of which occurred at least 18 days after discontinuation of study drug and were considered unrelated to treatment by the study investigator. One patient died of severe sepsis after receipt of active-comparator treatment of IV morphine (study IAP309) and the other died of acute renal failure after receipt of SST 15 µg (study ARX-C001; patient 4202). Patient 4202 was a 69-year-old white female who had an elective unilateral total knee replacement and died of acute renal failure 30 days after discontinuing SST 15 µg.

Laboratory findings

Safety laboratory assessments were not performed in the SST 30 µg studies SAP301, SAP302, SAP303, or SAP202. However, in SAP303, a screening blood sample was obtained from each patient to categorize the patient's renal and hepatic function, and AEs by renal and hepatic function are presented in Section 4.5 (Safety in special populations).

In the studies of SST 15 µg, no findings for clinical laboratory values or changes were considered clinically significant. Some laboratory assessment results were reported as AEs and were generally expected for this postoperative subject population and were not considered to be clinically meaningful. Rates of these AEs were comparable between the SST and placebo groups.

Safety in special populations

Safety related to drug-drug interactions and other interactions

AcelRx conducted 1 formal pharmacokinetic study (IAP104) assessing the effect of a CYP3A4 inhibitor (ketoconazole) on the SST. Co-administration of SST 15 µg and oral ketoconazole 400 mg resulted in effects on area under the curve (AUC), time to maximum plasma concentration (Tmax), and half-life (t½). There was only a small effect on maximum plasma concentration (Cmax) and no effect on context-sensitive half-time (CST½). Given the as-needed dosing schedule of the SST, the differences observed are unlikely to be clinically significant. However, proposed labeling contains a warning regarding concomitant use of the SST 30 µg with CYP3A4 inhibitors.

Additional drug interactions for sufentanil include the following:

• Central nervous system (CNS) depressants: The concomitant use of CNS depressants including barbiturates, benzodiazepines, neuroleptics or other opioids, halogen gases or other non-selective CNS depressants (eg, alcohol) may enhance respiratory depression.

• Monoamine oxidase (MAO) inhibitors: Discontinuation of MAO inhibitors is generally recommended 2 weeks before treatment with Zalviso, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Discontinuation due to adverse events

Pool 3 (ARX-04 Placebo-controlled Patient Pool)

In placebo-controlled studies of the SST 30 µg (Pool 3), AEs leading to discontinuation were experienced by 2 patients (1.4%) in the SST 30 µg group and 2 patients (2.7%) in the placebo group. No AEs leading to discontinuation occurred in more than 1 patient receiving SST 30 µg. Similarly to results for the Combined Placebo-controlled, All Patients Pool discussed above, there were few AEs leading to discontinuation.

Pool 2 (All ARX-04 Patient Pool)

AEs leading to discontinuation observed in all pooled studies of SST 30 µg (Pool 2)) were generally consistent with those observed in the placebo-controlled studies of SST 30 µg. In the SST 30 µg group, only 1 AE leading to discontinuation (oxygen saturation decreased in 2 patients [0.6%]) was experienced by more than 1 patient.

Pool 5 (Combined Placebo-controlled, All Patients Pool)

Overall, there were few AEs leading to discontinuation. AEs leading to discontinuation were experienced by 13 patients (3.6%) in the SST group and 6 patients (3.4%) in the placebo group and were consistent with expected AEs of opioid treatment and the postsurgical setting. In the SST group, the only AEs leading to discontinuation experienced by more than 1 patient were nausea and sedation in 3 patients (0.8%) each and respiratory rate decreased and anxiety in 2 patients (0.6%) each. See ISS Section 5.2.8.1 for additional discussion.

Comparison with Zalviso

Results were consistent across pooled patient populations, as the moderate and severe treatment-related AEs in all pooled groups were generally consistent with those expected of opioid treatment and the treatment settings. A somewhat higher rate of discontinuations due to AEs was observed in studies of SST 15 µg as compared to studies of SST 30 µg (7.1% for SST 15 µg vs. 1.9% for SST 30 µg and 2.7% for ARX-04 placebo vs. 5.8% for Zalviso placebo). This may be attributable to the longer study periods of the studies of SST 15 µg (up to 72 hours in Phase 3 studies and 12 hours in Phase 2 studies) as compared to studies of SST 30 µg (up to 48 hours in SAP301, 12 hours in SAP303 and SAP202, and 5 hours in SAP302). In addition, a generally younger population received the SST 30 µg and over half of the patients treated with SST 15 µg received a third dose in the first hour of treatment, which exceeds the dose of sufentanil received from the maximum SST 30 µg dosage of 1

tablet per hour (see ISS Section 10 for additional discussion, including comparison of AEs between patients who received 2 or 3 doses of SST 15 µg).

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5.5. Discussion on clinical safety

Sufentanil has been available in the EU since 1978, thus its safety profile, even in higher doses, is well established. As a mainly mu-agonist, sufentanil shares with morphine and fentanyl mu-receptor-mediated adverse drug reactions such as euphoria, sedation, respiratory depression and decreased bowel motility, as well as causes nausea and vomiting by excitation of the chemosensitive trigger zone.

In 2014, AcelRx presented Zalviso, a 15 µg sufentanil microtab combined with a PCA dosing system, which allowed patients to self-administer 15 µg sufentanil tablets sublingually after major abdominal/orthopaedic surgery. In Zalviso Phase-3 clinical studies, there were numerous patients, administering sufentanil doses very similar to that in the current application (i.e. 15 micrograms over 20-25 minutes). After justification of similarity of cmax values for the two different dosage regimens, Applicant used safety data obtained from these patients to support the present application.

Unlike Zalviso, the SST 30 µg was proposed to be administered only by HCPs in medically monitored settings, rather than “hospital settings only” used for Zalviso.

Baseline characteristics

Clinical studies included 686 patients in total, out of whom 363 patients were exposed to SST 30 µg, and 323 patients were exposed to 30-45 µg/hour doses of Zalviso SST 15µg.

Despite the proposed indication, majority of patients evaluated were post-operative, with an additional 76 patients who were presented at ERs with acute pain significant enough to warrant opioid analgesia.

The pooled database for the safety assessment of Sufentanil 30 µg SST includes SST 15 µg doses considered equivalent to SST 30 µg (2 SST 15 µg tablets dosed within 20 to 25 minutes of each other).

However, within the patients who received SST 15 µg, there was a subset (N = 243 of 323) who received a third dose of the SST 15 µg in the first hour of treatment, which exceeds the dose of sufentanil received from the SST 30 µg product per hour. AEs were more common in patients receiving the SST 15 µg (80.8% of patients experienced AEs) than in patients receiving the SST 30 µg (44.6% of patients experienced AEs). Inclusion of the SST 15 µg patients in the overall study database provides a conservative safety assessment since these patients were exposed to up to 45 µg of sufentanil in 1 hour.

Safety characteristics

Based on clinical study results and data from the published literature, including available safety information on the epidural route of Sufenta administration for labor analgesia, the conclusions for safety have been drawn.

The AE profile of the SST 30 µg was typical of opioid agonists, and no new safety issues were identified in studies of the SST. In placebo-controlled studies, the most common AEs included nausea, vomiting, headache, dizziness, pruritus, and somnolence.

The rate of SAEs was low, with 7 patients (5 SST and 2 placebo) out of 904 patients experiencing SAEs in pooled studies of the SST. SAEs included angina pectoris in a patient receiving SST 30 µg; oxygen saturation decreased, confusional state, hypoxia, pulmonary embolism, atrial fibrillation, and postoperative ileus in patients receiving SST 15 µg; and syncope and hemiparesis in patients receiving placebo.

There were few AEs leading to discontinuation. Across all placebo-controlled studies, AEs leading to discontinuation were experienced by 3.6% of patients in the SST group and 3.4% in the placebo group – practically similarly.

Across studies of the SST, mean changes from baseline in respiration rate were generally small and not clinically meaningful. In the placebo-controlled studies, 2 patients (0.6%) receiving the SST discontinued due to respiratory rate decreased and 1 each (0.3%) discontinued following oxygen saturation decreased and hypoventilation.

1.1% of patients receiving the SST in placebo-controlled studies had a lowest oxygen saturation value < 90%. Throughout the placebo-controlled studies, 92.2% of patients receiving the SST maintained oxygen saturation values > 93%, and 80.2% maintained oxygen saturation values > 95% with or without supplemental oxygen.

Comparing the SST to placebo, the mean (SD) lowest oxygen saturation in the SST group was 95.0% (3.4%), which is somewhat lower than that observed in the placebo group (95.7% [1.6%]; p=0.001). No naloxone use was required throughout the ARX-04 studies.

The published literature has been reviewed to inform the pregnancy and lactation labelling for the SST 30 µg. Sufentanil has been shown in published literature to cross the placenta, and cardiac effects have been observed in neonates whose mothers received epidural or intrathecal sufentanil during labor and delivery. Sufentanil has been reported to be excreted in human milk following epidural administration but had no apparent effects on newborn behaviour over 3 days postpartum in a published study.

Subgroup analysis

Safety analysis across *different population subgroups* (including assessments across age groups, sexes, races [Caucasian vs. non-Caucasian], BMI groups, ASA Classes, patients with varying organ function [hepatic and renal impairment], and surgery types) showed consistency with the known risks of opioids. Based on comparisons of AE rates, rates of AEs tended to be higher in older patient groups and were higher in women than in men. Rates of AEs were also higher in patients with a BMI < 30 kg/m2 than in patients with a BMI ≥ 30 kg/m2 and ≤ 40 kg/m2 and in ASA Class I patients than in ASA Class II patients, although the clinical significance of this, if any, is unclear.

Statistically significant differences in AE frequencies could be experienced for nausea and vomiting AEs *between SST 30 µg and placebo groups* for patients below 65 years of age, for both male and female patients, for Caucasian patients, for patients with BMI lower than 30 kg/m2, and for ASA class I patients.

The analysis of subgroups, such as the older age-groups, were not meaningful due to limited number of patients.

Interaction with ketoconazole

An interaction between sufentanil and ketoconazole, a CYP3A4 inhibitor, was seen in a pharmacokinetic drug-drug interaction study. Co-administration of SST 15 µg and oral ketoconazole 400 mg resulted in statistically significantly higher AUC0-last (60% increase) and AUC0-inf values (77% higher) for sufentanil in plasma compared to the corresponding values for SST 15 µg administered alone ($p < 0.001$ for each). While these differences are statistically significant, given the as-needed dosing schedule of the SST, they are unlikely to be clinically significant. Mean Cmax increased only by 19%, and median CST½ in the sufentanil plus ketoconazole group compared to sufentanil alone was not statistically significantly different.

2.5.6. Conclusions on clinical safety

The CHMP was of the opinion that the available safety data, including historical data for reference product, supported the Application for Dzuveo in the treatment of acute moderate to severe pain. Relevant safety data have been adequately reflected in the Risk Management Plan.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Respiratory depression Hypersensitivity
Important potential risks	Drug abuse and drug diversion Overdose Bradycardia Hypotension Paralytic ileus Spasm of the sphincter of Oddi Use in patients with raised intracranial pressure Convulsion
Missing information	Use during pregnancy and lactation Use in patients with hepatic impairment Use in patients with renal impairment Use beyond 48 hours

Pharmacovigilance plan

Table of On-going and planned additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Survey aiming at measuring the effectiveness of	The survey should contain questions on the actual use of Dzuveo, and assess whether the HCP followed the guidance	Respiratory depression	Study to be initiated 6 months to 2 years after	Study results to be submitted within 6

Table of On-going and planned additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
the risk minimisation measures (routine / additional) Planned Category 3	provided in the educational materials.	Overdose	launch of the product in selected medical centres across EU countries January 2020 is the estimated start date	months from completion of the survey. December 2020 is estimated completion date

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Respiratory depression	Routine risk minimisation measures: *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 5.1* *SmPC section 4.4 where advice is given on monitoring the respiratory effects* *PL section 2, 4* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimisation measures: *Healthcare Professional Guide*	Additional pharmacovigilance activities: *Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional)*
Hypersensitivity	Routine risk minimisation measures: *SmPC section 4.3, 4.8* *PL section 2, 4* *Prescription only medicine*	None
Drug abuse and drug diversion	Routine risk minimisation measures: *SmPC section 4.4*	None

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	Prescription only medicine	
Overdose	Routine risk minimisation measures: *SmPC section 4.4, 4.9* *SmPC section 4.9 where advice is given on management of overdose* *PL section 3* *PL section 3 where advice is given how to detect sign and symptoms of overdose* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimisation measures: *Healthcare Professional Guide*	Additional pharmacovigilance activities: *Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional)*
Bradycardia	Routine risk minimisation measures: *SmPC section 4.4, 4.5, 4.8, 5.1* *PL section 2, 4* *Prescription only medicine*	None
Hypotension	Routine risk minimisation measures: *SmPC section 4.4, 4.8* *PL section 2, 4* *Prescription only medicine*	None
Paralytic ileus	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Prescription only medicine*	None
Spasm of the sphincter of Oddi	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Prescription only medicine*	None

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Use in patients with raised intracranial pressure	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Prescription only medicine*	None
Convulsion	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4* *Prescription only medicine*	None
Use during pregnancy and lactation	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* *Prescription only medicine*	None
Use in patients with hepatic impairment	Routine risk minimisation measures: *SmPC section 4.2, 4.4, 4.8, 5.2* *SmPC section 4.4 where advice is given on monitoring the liver function* *PL section 2* *Prescription only medicine*	None
Use in patients with renal impairment	Routine risk minimisation measures: *SmPC section 4.2, 4.4, 4.8, 5.2* *SmPC section 4.4 where advice is given on monitoring the renal function* *PL section 2* *Prescription only medicine*	None
Use beyond 48 hours	Routine risk minimisation measures: *SmPC section 4.2, 5.1* *Prescription only medicine*	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.8.2. Labelling exemptions

A request to omit certain particulars from the immediate label (applicator label) as well as a request of translation exemption of the immediate label as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Dzuveo will be supplied as sublingual tablets in a single use applicator in a medically monitored setting.

The size of the applicator is rather small and the printable space very limited. Being an opioid, the product is to be used by a HealthCare Professional only in a controlled medical setting.

Apart from the space limitations, it was to be noted that the applicator will be included in a pouch which will display all required information, including route of administration, EXP and Lot. The applicator/tablet will have to be used immediately once removed from the pouch and this is reflected by the statement ‘Administer product immediately after opening pouch’ added on the pouch label.

The particulars agreed to be printed in English only on the immediate label are:

Dzuveo 30 mcg sublingual tablet
sufentanil
Lot

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language as agreed by the QRD Group.

The applicant is also requested to include in the translated version of the package leaflet a reference to the name of the pharmaceutical form in English (in brackets), in section 6.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Sufentanil 30 µg sublingual tablet is indicated for the management of acute moderate to severe pain in adult patients.

3.1.2. Available therapies and unmet medical need

Other available therapies include other opioids, in most cases given parenterally.

The rationale for delivering sufentanil sublingually is that by using the sublingual space as a drug depot, the drug uptake occurs over time, resulting in a sublingual CST½ (median = 2.3 hours) that provides a more appropriate duration of analgesia compared to IV administration (median CST½ = 6 minutes).

3.1.3. Main clinical studies

Efficacy of SST 30 µg was demonstrated in 2 randomized, double-blind, placebo-controlled studies (SAP301 and SAP202) in a total of 221 patients (SST 30 µg, n = 147; placebo, n = 74) treated for up to 12 or 48 hours. Further support for the clinical utility of SST 30 µg was provided by 2 open-label Phase 3 studies (SAP302 and SAP303) conducted in a total of 216 patients (76 patients presenting to the Emergency Department and 140 post-surgical patients). Support for the efficacy of SST 30 µg compared to an active comparator is provided from an analysis of data from the active-controlled Phase 3 study IAP309 conducted in support of the Zalviso product.

SAP202 was a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the Sufentanil Nanotab® for the management of acute pain following bunionectomy alone or with hammertoe repair. Patients selected were 18 to 80 years old, the study population was representative to the whole human population in terms of age and gender. The total ITT population number was 100 disposed in three treatment arms (placebo, 20µg sufentanil, 30µg sufentanil).

SAP301 was a multicentre, randomized double-blind, placebo-controlled trial to evaluate the efficacy and safety of the Sublingual Sufentanil Tablet 30 µg in adult patients who had undergone an ambulatory abdominal surgery normally performed as an outpatient procedure: abdominoplasty; open-tension-free inguinal hernioplasty (Lichtenstein repair with mesh); or laparoscopic abdominal surgery. A total of 163 patients (109 sufentanil, 54 placebo) were enrolled and randomized in this study; two patients (both in the sufentanil group) did not receive study drug, leaving 161 patients who received study drug and were included in the ITT and safety populations. The patients were 18 years or older, the study was imbalanced in terms of gender and white population was overrepresented. There were approximately double number of women than men.

3.2. Favourable effects

The primary benefit of SST 30 µg is its efficacy in management of moderate to severe acute pain. The primary efficacy endpoint was the time-weighted summary of pain intensity difference in the first 12

hours (SPID12) after surgery. In both main studies 30µg sublingual sufentanil was superior to placebo. (In SAP202 LS Mean difference of SPID12: 13.66, 95% CI for difference 4.79, 22.52, p-value: 0.003; in SAP301 LS Mean difference: 12.70 (2.80), 95% CI for difference: 7.16, 18.23, p-value<0.001)

Secondary efficacy endpoints of clinical relevance were total pain relief, pain intensity, pain intensity difference and use of rescue medication. These parameters supported the result in the primary efficacy endpoint.

Data are consistent with those obtained from the clinical efficacy studies of Zalviso.

3.3. Uncertainties and limitations about favourable effects

The connection between the plasma levels and the therapeutic effect was poorly defined. The SST 30 µg tablets should be taken on an on demand basis, but it is not clear which extrinsic and intrinsic factors govern and influence the patients' requests for additional doses. Pain intensity data were also imputed after rescue medication but additional analyses showed that even an imputation under a worst-case scenario preserves the clinical and statistical significance of the results.

SAP202 was originally designed as a dose-finding study therefore the sample size was too small to establish feasible subpopulation analyses.

The sample size was small to see analgesic effect in patients over 65 years in both main studies.

In SAP301 there were too few male patients to see superior analgesic effect to placebo in the subgroup analysis.

The product was investigated in double-blind placebo-controlled trials against postoperative pain only. Other acute pain situations were present in one open-labelled study SAP302 without active comparator.

3.4. Unfavourable effects

Sufentanil has been available for clinical use since 1978 in the EU, thus its safety profile including the adverse event profile and the abuse potential is well established even in higher doses than the ones used for the current application (30 µg).

Common sufentanil related adverse events were also seen in Sufentanil 30 µg SST clinical trials. Most frequent of treatment-related adverse events in the SST 30 µg group (=sufentanil related adverse events) were nausea (36.7%), vomiting (11.6%), dizziness (9.5%), headache (8.2%), somnolence (6.8%), hypotension (3.4%), pruritus (2.7%), in the SST 30µg placebo-controlled clinical studies (ARX-04 Placebo-controlled safety data pool, Pool 3), and nausea (26.7%) and vomiting (5.8%) in All ARX-04 clinical studies (All ARX-04 safety data pool, Pool 2).

Respiratory events, including decreased oxygen saturation, which is always a concern in opioid therapy was experienced in two cases in Pool 3 clinical studies. However, one of them was a respiratory rate decreased AE, which was considered a severe one and led to discontinuation of the concerned patient from the study.

These effects necessitate the restriction of use of the Sufentanil 30µg SST to a medically monitored setting, where these potentially life threatening events can be recognized and controlled adequately in a timely manner. This means a somewhat narrower use than the proposed one (i.e. a medically supervised setting).

A pooled safety analysis was also carried out for placebo-controlled sufentanil SST 30µg studies together with placebo-controlled Zalviso studies (=safety data pool Pool 5). A subset of patients taking 30-45 µg sufentanil (=2-3 Zalviso 15 µg microtabs) during one hour from placebo-controlled Zalviso studies was included into Pool 5. Safety findings for Pool 5 was similar to tha observed in Pool 3 in AEs and AE frequencies.

Comparison of safety profile of Sufentanil 30 µg SST with Zalviso Phase 2 and Phase 3 safety data pool (=Zalviso comparison Pool) showed a more favourable safety profile for Sufentanil 30 µg SST in AE/ SAE rate and AE severity.

3.5. Uncertainties and limitations about unfavourable effects

Co-medication data were presented in a rather general manner in the submitted Summary of Clinical Safety and Integrated Safety Summary documents, explicit concomitant medication data were included into patients' CRFs only.

Analysis of effect of concomitant medication, including an eventual perioperative opioid medication (if any) on safety findings was not presented. Incidence of patients requiring rescue therapy as well as rescue medications used in ARX-04 studies were different, e.g. proportion of patients not requiring rescue medication varied from 30.0% (SAP202) to 85.7% (SAP303, total). This variability further complicated the definition of the safety characteristics of Sufentanil 30 µg SST.

AE rate was found lower for patients with BMI between 30 and 40 kg/m^2 than for BMI <30 kg/m^2 for ARX-04 (SST 30 µg) data pools (Pool 2 and Pool 3) as well as in SST 30 µg-Zalviso combined data pool (Pool 5) and Zalviso data pool. This is an interesting phenomenon, since the opposite one would be expected from clinical point of view. AE observations for BMI subgroup of >40 kg/m^2 should be handled with caution because of the low patient number in this BMI subgroup.

Safety data for patients ≥75 years of age also are limited, since there were only 8 of them in All ARX-04 Patient Pool (Pool 2) and 60 of them were included into Combined Placebo-controlled patient pool (Pool 5).

In the Phase 3 trials, the therapeutic sufentanil levels were significantly below what is the potentially achievable level with hourly dosing. Because of lower than maximally achievable plasma levels the safety data might underestimate the risk when the SST 30 µg tablets are administered as frequently as the SmPC allows.

3.6. Effects Table

Table X. Effects Table for sufentanil

Effect	Short Description	Unit	Treatment	Result	Uncertainties / Strength of evidence	References
Favourable Effects						
Pain reduction	SPID12 mean difference vs placebo		Sufentanil Placebo	13.66	p-value: 0.003	SAP202

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
	SPID12 mean difference vs placebo		Sufentanil Placebo	12.70	p-value<0.001	SAP301
Unfavourable Effects						
nausea		%	Sufentanil	36.7		Phase III
vomiting		%	Sufentanil	11.6		Phase III
dizziness		%	Sufentanil	9.5		Phase III
headache		%	Sufentanil	8.2		Phase III
somnolence		%	Sufentanil	6.8		Phase III

Abbreviations: SPID-12: summed pain intensity difference over the 12-hour study period

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Moderate to severe acute pain in post-operative patients occurs frequently and is often difficult to treat effectively or is undertreated. Despite substantial advances in the knowledge of acute pain mechanisms, post-operative pain is still under-managed. Strong opioids such as morphine, fentanyl, or oxycodone, are recommended by the World Health Organization (WHO) as part of the analgesic pain ladder for the management of moderate to severe pain conditions (WHO 1996), at least as part of a multi-modular pain regimen.

As this product is administered in a non-invasive way, the burden with injection/infusion is avoided which might make pain control easier. A non-invasive route of administration may be especially relevant when the availability of IV access may be limited, such as by a patient's physical location in an emergency trauma situation or by difficulty in accessing veins in patients in shock due to vasoconstriction or in obese, elderly, burn, and needle-phobic patients.

Although subpopulation analyses were in some cases impossible (effect in elderly patient) or negative (male patients in study SAP301), based on previous results from Zalviso efficacy studies and on the general patterns of well-known opioids it is unlikely that age or gender would have high impact on the effectiveness of sufentanil.

The unfavourable effects are those typical to opioids therefore well-known and predictable. One typical unfavourable effect characteristic to this product can be the consequence of swallowing the sublingual tablet: this may result in incomplete absorption of the active substance therefore decreased or absent efficacy.

3.7.2. Balance of benefits and risks

Sufentanil is a well-known opioid which showed efficacy in postoperative settings after visceral and orthopaedic surgery when administered sublingually as SST NanoTab 30µg.

The effects and adverse effects are predictable, based on previous experience with other opioids and with a similar product Zalviso.

3.8. Conclusions

The overall B/R of Dzuveo 30 mcg sublingal tablet for the management of acute moderate to severe pain in adult patients is positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dzuveo is favourable in the following indication:

Dzuveo is indicated for the management of acute moderate to severe pain in adult patients.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of Dzuveo in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where Dzuveo is marketed, all HCPs (i.e. physicians, hospital pharmacists, and nurses) who are expected to prescribe / administer the product are provided with a Healthcare Professional Guide, outlining critical information for the safe and effective use of Dzuveo, including:

- The method of use of the device;
- The minimum dosing interval of one sublingual tablet per hour, in order to prevent / minimise the important identified risk of respiratory depression and the important potential risk of overdose;
- The key message to convey during patients counselling, about possible respiratory depression / overdose;
- Detailed instruction on how to handle overdose / respiratory depression

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.