EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/612007/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zalviso

International non-proprietary name: sufentanil

Procedure No. EMEA/H/C/002784/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AAC	Authorized Access Card
AAMI	Association for the Advancement of Medical Instrumentation
ASMF	Active substance master file
AUC	Area under the concentration-time curve
AUC0-inf	Area under the concentration-time curve from time zero to infinity
AUC0-t	Area under the concentration-time curve from time zero to time of last measurable concentration
AUCNRS	Area under the response curve of the NRS sedation assessment at a given time point
AUCRASS	Area under the response curve of the RASS sedation assessment at a given time point
BMI	Body mass index
BOCF	Baseline observation carried forward
CE	Conformité Européene
CHMP	Committee for Medicinal Products for Human use
Cmax	Maximum concentration
CNS	Central nervous system
CQA	Critical Quality Attribute
CST½	Context-sensitive half-time
CV	Coefficient of variation
CYP	Cytochrome P450
DoE	Design of experiments
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
HPGA	Health professional global assessment
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IMP	Investigational medicinal product
IPC	In-process control
IR	Infrared spectroscopy
ITT	Intent-to-treat
IV	Intravenous
IV PCA	Intravenous patient-controlled analgesia
LDPE	Low density polyethylene
LOCF	Last observation carried forward
LOD	Loss on drying
NMR	Nuclear magnetic resonance
NRS	Numeric rating scale
PCA	Patient-controlled analgesia
PGA	Patient global assessment
Ph. Eur.	European Pharmacopoeia

PRN	Pro re nata; self-administered as needed
QbD	Quality by design
RASS	Richmond Agitation Sedation Scale
RFID	Radiofrequency identification
RH	Relative humidity
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SPID	Sum of pain intensity differences
SPRID	Time-weighted summed PR intensity differences
SSM	sufentanil sublingual microtablet
SSMS	sufentanil sublingual microtablet system
SST	Sufentanil sublingual tablets
SSTS	Sufentanil sublingual tablet system
t½	Half-life
t½ke0	plasma/CNS equilibration half-life
Tmax	Time to Cmax
Tmax-norm	time from maximum sedation to normal (RASS=0 or NRS=0)
TmaxNRS	time to maximum sedation based on NRS assessment
TmaxRASS	time to maximum sedation based on RASS assessment
Tsedate	total duration of sedation
TOTPAR	Total pain relief
US	United States
WHO	World Health Organization
WOCF	Worst observation carried forward
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Grunenthal GmbH submitted on 25 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zalviso, 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 20 September 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical 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 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:

Zalviso is indicated for the management of moderate to severe acute pain in adult patients in a medically supervised environment.

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 and appropriate non-clinical and clinical data.

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.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Sufenta Forte solution for injection 0.05 mg/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 solution for injection 0.005 mg/ml
- Marketing authorisation holder: Janssen-Cilag B.V.
- Date of authorisation: 01-11-1978
- Marketing authorisation granted by:

☐ Member State (EEA): Netherlands

- National procedure

- Marketing authorisation number: RVG 09232

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

An application was filed in the following country: United States.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Milena Stain

Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 25 June 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 10 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014.
- PRAC RMP advice and assessment overview were adopted by PRAC on 6 November 2015.
- During the meeting on 20 November 2014, 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 12 March

2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 April 2015.
- PRAC RMP advice and assessment overview were adopted by PRAC on 7 May 2015.
- The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality assessment of the product:

  A GMP inspection at Patheon Pharmaceuticals Inc. 2110 E. Galbraith Road Cincinnati, Ohio 45237 USA between 19-22 January 2015 by the National Competent Authority of Germany (positive outcome).
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 June 2015.
- Joint Rapporteur's preliminary assessment report on the MAH's responses was circulated on 30 June 2015.
- PRAC RMP advice and assessment overview were adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, 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 Zalviso.

2. Scientific discussion

2.1. Introduction

Problem statement

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 (Huang et al. 2001, Gan et al. 2014).

Insufficient post-surgical pain relief is of concern as under-treatment of post-operative pain can result in life-threatening adverse events, such as pneumonia or deep vein thrombosis and pulmonary embolism, when pain limits deep breathing and mobility. Over-treatment of pain can result in a heavily sedated patient who is then at risk for oxygen desaturation and respiratory depression, especially when utilizing opioids and other central nervous system (CNS)-depressant drugs (Pattinson 2008).

A modern concept of opioid treatment in acute pain conditions is for the patient to self-administer an adequate opioid dose, as needed, to titrate themselves to tolerable pain levels in a medically supervised environment. The opioid is administered intravenously via a programmable pump that is kept at the patient's bedside. This concept of intravenous patient-controlled analgesia (IV PCA) with opioids has been shown to provide higher patient satisfaction compared to pain regimens in which analgesics were routinely administered to prevent pain or in which nurses assisted administration of analgesics according to patients' demand when their pain became intolerable (Thomas et al. 1995, Ballantyne et al. 1993). Even though the benefits of IV PCA are recognized, the complexity associated with ordering, dispensing,

preparing, programming, and administering opioids via an IV PCA pump results in many analgesia-related errors and restrictions. The most common errors associated with IV PCA are wrong dose (38.9%), wrong drug (18.4%), omitted drug (17.6%), prescription error (9.2%), wrong administration technique (4.8%), and extra doses administered (4.7%) (Moss 2010).

About the product

Sufentanil is a well-known potent, opioid analgesic with a fast onset of action. The rapid equilibration with effector sites in the CNS, high therapeutic index and lack of active metabolites would appear to make it an optimal opioid for treating acute pain. Thus, patients can be more safely titrated to an effective analgesic dose before dose limiting side effects or even life-threatening respiratory depression occurs. Sufentanil allows for rapid transmucosal uptake due to its lipophilic properties, resulting in a quick onset of pain relief.

Due to significant first-pass metabolism, sufentanil has a low oral bioavailability. Therefore, a sublingual route of delivery was chosen by the applicant as an alternative to an intravenous route of administration..

Zalviso sublingual tablets are to be self-administered using the administration device which should only be actuated by the patient in response to pain. Zalviso sublingual tablets are to be administered in a hospital environment which ensures immediate access to health care professionals able to manage opioid adverse reactions, particularly respiratory depression.

The Zalviso administration device is designed to deliver a single sufentanil 15 micrograms sublingual tablet, on a patient-controlled as needed basis, with a minimum of 20 minutes (lockout interval) between doses.

Zalviso administration system

The Zalviso administration system has been assessed by the British Standards Institute. The CE Mark has been granted o 27 Nov 2014. The main medical device components of SSTS are:

- Reusable Controller, a hand-held, rechargeable unit with all electronics, motor and other parts, and software for SSTS.
- Single-patient use (disposable) Dispenser that allows for placement of SSTS via ergonomic geometry for optimal sublingual delivery. The dispenser also has a cap to cover the Dispenser tip in between dose administrations.
- Single-dosage strength (disposable) Drug Cartridge that contains a tamper-evident priming cap and 40 SSTs and serves to protect the tablets during storage and patient usage.
- Reusable security Tether that is used to secure SSTS to the patient's bedside or wheelchair.
- Reusable Holster to hold SSTS when not in use by the patient.
- Secure access system comprised of a disposable wireless, electronic, adhesive Patient identifier (ID) Thumb Tag containing radiofrequency identification (RFID) to pair a unique patient to a specific SSTS and a separate reusable wireless Authorized Access Card (AAC) for the healthcare professional. The healthcare professional must use the AAC in order to set up SSTS for a new patient, change a Drug Cartridge, move the security tether, or discontinue therapy.

During set-up, which is completed by a healthcare professional, a Drug Cartridge is inserted into a Dispenser, which is then locked into the Controller. The patient places the Dispenser tip under his or her tongue, and depresses the Controller Dose Button to administer a SST 15 µg as needed based on a fixed 20-minute lockout period. The Patient ID Thumb Tag, a healthcare professional AAC, and a security

Tether help to ensure that only the intended patient can self-administer the analgesic medicine as needed for pain control.

Type of Application and aspects on development

This Application for a marketing authorisation of Zalviso 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 Zalviso 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.

The Applicant did not conduct any clinical studies against the reference product. This was justified by the Applicant by the differences in the strength, daily dose, route of administration and indication. The Application for Zalviso only referred in certain areas to Sufenta, in particular to non-clinical data, and in all these areas there was no need for bioequivalence or comparable bioavailability studies to the reference product. Comprehensive clinical data were generated by the Applicant to support the safe use of Zalviso for patient controlled analgesia in the proposed indication. For these reasons, the CHMP agreed that no studies against the reference product were necessary.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as sublingual tablets containing 15 μg of sufentanil (as citrate salt) as active substance.

Other ingredients are mannitol (E421), anhydrous calcium hydrogen phosphate, hypromellose, croscarmellose sodium, stearic acid, magnesium stearate and Sunset Yellow Aluminium Lake (E110).

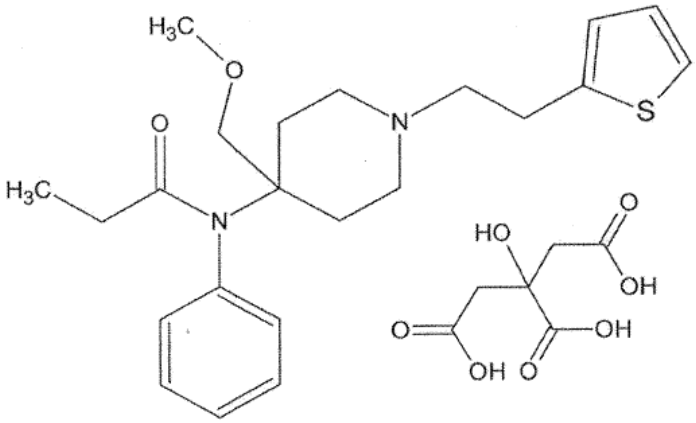
The product is available in a polycarbonate cartridge containing 40 tablets, packed inside a polyester film/LDPE/aluminium foil/LDPE sachet with oxygen absorber.

The product should only be used with the Zalviso administration device which consists of a controller and dispenser, essential for its safe and proper use. The disposable cartridge fits into the disposable dispenser which is in turn inserted into the re-usable pre-programmed electro-mechanical controller. This allows the patient to self-administer tablets in response to pain, but prevents over-dosing by limiting the frequency at which tablets can be dispensed.

2.2.2. Active substance

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 and it has the following structure and properties:



Molecular formula: $C_{22}H_{30}N_2O_2S.C_6H_8O_7$ - Relative molecular mass: 587.7 $gmol^{-1}$

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 solid, soluble in water and sparingly soluble in ethanol and acetone. Two polymorphic forms of the active substance are known. Neither polymorphic form nor particle size is considered important for the finished product quality due to the current finished product manufacturing process.

Sufentanil citrate is achiral.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF.

Sufentanil citrate is synthesized by a single manufacturer. The starting materials were re-defined during the procedure in order to address a major objection and their specifications are considered acceptable. All critical steps of the synthetic process are now described in the dossier.

The characterisation of the active substance and its impurities is 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 specification of the finished product manufacturer includes tests for appearance, identity (IR), assay (titration), impurities (HPLC), loss on drying (Ph. Eur.) 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 eight production batches of active substance from the proposed manufacturer stored in 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), impurities and degradation products. The analytical methods used were the same as for release, other than the additional HPLC assay method, 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. There is likely little impact of dosing of sufentanil free base 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 is 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, protected from oxidants.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Zalviso was developed in order to produce an orally available formulation of the opioid analgesic and sedative sufentanil, used in intravenous anaesthetic regimens in operating theatres. Given the dangers of overdosing on sufentanil, the product is accompanied by a device which allows the patient to self-medicate in response to pain. Once a tablet has been administered, the device enters a lockout phase which prevents a further tablet being administered for 20 minutes, thus preventing overdose.

Sufentanil is highly potent and thus constitutes only a minor proportion of the finished tablet composition. In order to ensure content uniformity, a solution of active substance is combined with the excipients during formulation in order to ensure an even distribution. Several polymorphic forms of sufentanil are known. Tablets manufactured using different polymorphic forms of sufentanil were made and their dissolution profiles demonstrated to be equivalent. Thus, the polymorphic form as well as the particle size are not considered important for the product manufacture due to the described finished product manufacturing process and hence do not need to be controlled.

Sufentanil has low oral bioavailability due to significant first pass metabolism. Despite being soluble in water, it is highly lipophilic, allowing for rapid trans-mucosal uptake and a quick onset of action. Thus, the sublingual route of administration was chosen. A small tablet size was sought in order to minimize patient saliva response, but this also had to be compatible with the device and delivery mechanism. Rapid tablet erosion was also required to afford patients a rapid analgesic response. Finally, adequate bioadhesion of

the tablet to the sublingual cavity was necessary to prevent swallowing of the tablet which would result in reduced efficacy.

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.

The original dry granulation process resulted in poor content uniformity so a wet granulation method was developed instead. Some of these studies were carried out using a substitute active substance instead of sufentanil, given the latter's high potency and thus the exposure risk for investigators. This is considered acceptable given the low active substance content and similar solubilities of the two active substances in the granulation liquid. Results were later confirmed using sufentanil citrate.

The critical quality attributes (CQAs) of the product were identified as assay, purity, stability, content uniformity, dissolution and device compatibility. A risk assessment was carried out in order to identify potential critical process parameters for all steps of the manufacturing process. A combination of multi-variate (via DoEs) and univariate experiments were carried out in order to assess ranges of process parameters for high and medium risk operations, but none were identified as critical. No design space is claimed for this product. Set-points and ranges have been set for compression force and speed which can be altered in response to the results of in-process controls (IPC) for tablet weight and resistance to crushing. Performance of the product with the device is ensured by an IPC for friability, given the thinness of the tablet.

Early clinical batches were manufactured on small scale and thus were not fully representative of the commercial formulation. However, since phase III clinical and pharmacokinetic studies were carried out with the intended commercial formulation, no bioequivalence studies were considered necessary.

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 1.5% sufentanil citrate is applied to compensate for an apparent loss in assay during the manufacturing process. The loss of active substance has been investigated and although no root cause has been found, it seems likely that losses occur during the granulation step. This is considered acceptable at the moment, given that the assay method has been shown to pick up changes in active substance content. However, it is recommended that the applicant conducts further investigations to identify the reason for the loss in potency during manufacture. In addition, the applicant should evaluate the assay of the first ten commercial batches produced with an overage of 1.5% and submit a variation in order to delete the overage in case the evaluation results in the conclusion that the overage is not needed. Furthermore, an additional IPC on content uniformity after compression should be performed on the first ten commercial batches and a comprehensive discussion of the results generated should be provided.

The primary packaging is a polycarbonate cartridge, each of which contains 40 sublingual tablets and is packed in a polyester film/LDPE/aluminium foil/LDPE sachet with an oxygen absorber. Each cartridge is tagged with a radio frequency identification (RFID) label. The materials 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 cartridge is intended to be inserted into a disposable dispenser which is in turn inserted into a reusable pre-programmed electro-mechanical controller which allows the patient to self-administer Zalviso in response to pain, without overdosing. The device has been assessed according to Medical Device Directive 93/42/EEC and has been granted a CE mark.

Manufacture of the product and process controls

The manufacturing process consists of four main steps consisting of wet granulation and drying, blending with extra-granular excipients, compression to form tablets, and packaging. The process is considered to be a non-standard manufacturing process since the active substance content is so low. Process validation was performed by manufacture of three consecutive commercial scale batches of Zalviso. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate to ensure the quality of Zalviso tablets. A test for LOD is carried out after wet granulation, and tablets are checked for weight, thickness, resistance to crushing and friability following compression. Additionally, the integrity of the sachets is checked once sealed.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identification (HPLC, 2 separate methods), assay (HPLC), uniformity of dosage units (Ph. Eur.), purity (degradants by HPLC), dissolution (Ph. Eur.), residual ethanol (GC), microbial contamination (Ph. Eur.) and tablet singulation (visual inspection).

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 identification and assay testing has been presented.

Batch analysis results are provided for four commercial scale batches used in stability, non-clinical and clinical studies, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on four commercial scale batches of finished product stored for up to 36 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 are identical, including the primary packaging, to those proposed for marketing. Samples were tested for description, assay, purity, dissolution and microbial contamination. Tablet singulation was tested at later time-points following introduction of the test to the release specifications. The analytical procedures used are stability indicating. No significant trends were observed to any of the tested parameters which remained within the specification limits.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, resulting in a decrease in assay and increase in impurities. Zalviso is thus considered to be photosensitive. The chosen commercial packaging was demonstrated to provide adequate protection from light.

An in-use stability study was conducted in order to assess the stability of the product once outside of the foil sachet. Three commercial scale batches were stored at 25 ^{o}C / 60% RH and 40 ^{o}C / 75% RH for up to 1 month and all tested parameters were well within specification. Given that the declared use of the product is for 72 hours only, in-use stability is considered to have been adequately demonstrated.

Based on available stability data, the shelf-life of 3 years stored in the original package to protect from light as stated in the SmPC is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetable origin.

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. A CE certificate was provided for the delivery device. 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.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space has been claimed.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should evaluate the assay of the first ten commercial batches produced with an overage of 1.5% and submit a variation in order to delete the overage in case the evaluation results in the conclusion that the overage is not needed.
- An additional in-process control on content uniformity after compression should be performed on the first ten commercial batches and a comprehensive discussion of the results generated should be provided.

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, based on intravenous, intrathecal and subcutaneous administration. 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.

The overview of the non-clinical program for Zalviso is presented in Table 1.

Table 1: Non-clinical program for sufentanil 15 µg sublingual tablets

Study type	Route of administration	Frequency of dosing	Species	GLP compliance
Pharmacokinetics				
Absorption	i.v. sublingual tablets	Single dose 5 administrations on 3 consecutive days	Dog	No
Absorption	i.v. sublingual p.o.	Single dose 2 administrations with a 3-days washout 2 administrations with a 1-day washout	Dog	No
Absorption	sublingual buccal	2 administrations with a 3-days washout 2 administrations with a 6-days washout	Dog	No
Toxicology				
Repeat-dose	buccal	Once daily for 7 days	Hamster	Yes
Repeat-dose	buccal	Once daily for 28 days	Hamster	Yes
Local tolerance	buccal	One or 5 administrations** / day for 1 day	Hamster	Yes
Local tolerance	buccal	Five administrations* / day for 4 days	Hamster	Yes

* Prior to dosing, the animals received naltrexone s.c.
** Prior to dosing, the animals received naltrexone or placebo s.c.

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. This might be due to different absorption pathways. Another factor which is important regarding kinetics is the site where tablet is disposed to. It did not influence the extent of absorption but after buccal administration the C_{max} 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

Due to the new formulation and the new route of administration, bridging studies up to 28 days were conducted in hamster. The local tolerance was also tested in hamster. The summary of the studies is presented in Table 2 below.

Table 2: Toxicological bridging program with sublingual sufentanil

Study type	Route of administration	Duration of dosing	Species	GLP compliance
Repeat-dose toxicity	Cheek pouch	7 days	Hamster	Yes
	Cheek pouch	28 days	Hamster	Yes
Local tolerance	Cheek pouch	1 day	Hamster	Yes
	Cheek pouch	4 days	Hamster	Yes

Single dose toxicity

None conducted.

Repeat dose toxicity

Sufentanil was evaluated in repeat dose studies in Golden Syrian hamster with buccal administration for 7 days at doses up to 320 µg/day or 28 days at doses up to 180 µg/day. Hamsters did not tolerate the 320 µg/day dose and were euthanized after 1 day of dosing. 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 haematocrit were observed, suggestive of hemoconcentration due to dehydration. No significant effects on clinical chemistry, organ weight, gross necropsy or histopathology were observed. No local effects were observed in this study either. All effects were reversible during the recovery period. It was concluded that the pharmacological and toxicological effects of sufentanil sublingual tablets were typical of what would be expected from an opioid agonist.

A NOAEL of 180 µg/day has been established for the 28-day toxicity study, with $AUC_{0\text{-last}}$ and C_{max} values of 200 ng.h/mL and 27.6 ng/mL on study day 0 and 82.7 ng.h/mL and 16.5 ng/mL on day 27. No additional target organs were identified in doses up to the MTD (180 µg/day).

The systemic exposure to sufentanil in 28 day repeat dose toxicity study was greater than that observed in the clinical study with the highest sufentanil daily dose. According to the mean $AUC_{0\text{-last}}$ animal/human ratio measured in 28 day repeat dose toxicity study, the level of exposure in the animal studies was more than 1000 fold than in the human clinical trials.

Genotoxicity

No genotoxicity studies were conducted with sufentanil.

The applicant identified four impurities derived from synthesis of sufentanil, which were either evaluated for genotoxic risk in Ames tests, by established QSAR methods or qualified due to its existence as metabolite of sufentanil and fentanyl. None of the identified impurities would be considered a genotoxic risk according to the proposed specification limit of 0.5%.

Carcinogenicity

None conducted.

Reproduction toxicity

None conducted.

Toxicokinetic data

Toxicokinetics data for the 7-day study are presented in Table 3.

Table 3: Toxicokinetics data

Daily dose (µg]	AUC_{last} (ng·h/mL)		C_{max} (ng/mL)		T_{max} (h)		$T_{1/2}$ (h)	
	Day 0	Day 6	Day 0	Day 6	Day 0	Day 6	Day 0	Day 6
15	18.4	18.9	6.51	7.87	1	1	5.4	n.r.
30	44.1	33.1	5.76	8.24	2	1	3.2	9.0
80	137	103	14.5	14.0	4	1	5.2	4.7
160	284	121	23.4	53.0	2	1	4.1	n.r.
320	640	-	57.8	-	4	-	6.4	-

n.r. not reportable

All male hamsters dosed buccally via the cheek pouch with Sufentanil Sublingual NanoTabs™ were systemically exposed to sufentanil. In terms of AUC_{last} and C_{max}, exposure increased with increasing dose over the 15 to 320 µg/day range on study day 0 and over the 15 to 160 µg/day range on study day 6, with exceptions for C_{max}, which was similar at 15 and 30 µg/day on both sampling days. On study day 0, exposure, in terms of AUC_{last}, increased more than proportionally to the increase in dose over the 15 to 320 µg/day range; in terms of C_{max}, exposure to sufentanil increased less than proportionally from 15 to 30 µg/day and proportionally from 30 to 320 µg/day. On study day 6, the relationship between dose and exposure was slightly less than proportional for both parameters over the 15 to 160 µg/day range. Exposure (AUC_{last}) was similar between sampling days at 15, 30, and 80 µg/day, but at 160 µg/day, exposure decreased about 2-fold from study day 0 to study day 6. The T_{max} for sufentanil was 1 hour post-dosing for all dose levels on study day 6 and ranged from 1 to 4 hours post-dosing on study day 0, with no clear trend related to dose level. Half-life ranged from approximately 3 to 6 hours on study day 0. On study day 6, reportable half-life values were approximately 5 and 9 hours for the 80 and 30 µg/day dosages, respectively.

Based on the results of this study, it was decided that the following 28-day study will use doses up to 180 µg/day.

Toxicokinetics data for the 28 day study is presented in Table 4 below.

Table 4: Toxicokinetics data

	AUC_{last} (ng·h/mL)		C_{max} (ng/mL)		T_{max} (h)		$T_{1/2}$ (h)	
	Day 0	Day 27	Day 0	Day 27	Day 0	Day 27	Day 0	Day 27
15	20.6	14.2	4.64	3.20	0.88	2.0	4.4	4.0
90	172	50.1	19.1	11.3	4.0	1.5	4.3	n.r.
180	200	82.7	27.6	16.5	0.75	1:5	4.8	4:6

n.r not reportable.

Toxicokinetic analysis suggests that sufentanil exposures (AUC_{last} and C_{max}) were roughly dose proportional. Sufentanil exposures on day 27 were lower at 90 and 180 µg/day than on day 0.

Although the study report states that 180 µg/day was a no observed adverse effect level (NOAEL), based on effects on body weight and clinical signs, it was determined that the maximum tolerated dose (MTD) for sufentanil administered buccally to hamsters is 180 µg/day.

Local tolerance

The applicant conducted one pilot (dose range finding) and one pivotal study to examine local tolerance of Sufentanil sublingual tablet after buccal administration in Golden Syrian hamster by s.c. pretreatment with the opioid antagonist Naltrexone. The dose range finding study (692063) established a 10 mg/kg Naltrexone dose as suitable to inhibit opioid effects of 400 µg/day sufentanil administered into the cheek pouch. The pivotal study on local tolerance of Sufentanil sublingual tablet (692032) showed exclusively treatment related, but no test-article related local effects on cheek pouch pathology or histopathology after 100 or 400 µg daily exposure with sufentanil for 4 days.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline. Sufentanil PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore sufentanil is not expected to pose a risk to the environment.

Based on the available data, no adverse environmental effects were anticipated with the use of Zalviso and the CHMP considered that a Phase II (Tier A) environmental fate and effect analysis was not required.

Table 5: Summary of main study results

Substance (INN): Sufentanil			
CAS-number (if available): 60561-17-3			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107	3.45	Potential PBT (N)

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.45	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)	0.0054	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			None

2.3.6. Discussion on non-clinical aspects

Sufentanil is a synthetic µ opioid receptor agonist that has been used in anaesthesiology for decades. Non-clinical pharmacology, pharmacokinetics and toxicology including the primary effect 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 referred to the approved information of the reference product Sufenta, published literature and provided a package of studies focused on transmucosal administration of sufentanil.

2.3.7. Non-clinical data reveal no special hazard for humans.

The SmPC is fully in line with the data presented in the non-clinical part of the submitted documentation.
Conclusion on the non-clinical aspects

The submitted non-clinical data support the clinical use of sublingual sufentanil in the management of post-operative pain. Cross-references to Sufenta as well as published data in the scientific literature were considered adequate by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for sublingual tablets containing sufentanil. To support the marketing authorisation application the applicant conducted a dedicated clinical program as presented in Table 6 below. In addition, cross-references to Sufenta and published literature were made with regard to primary and secondary pharmacodynamics and safety.

Table 6: Tabular overview of clinical studies

1 TABULAR LISTING OF ALL CLINICAL TRIALS

Type of trial	Trial identifier	Location of trial report	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects enrolled; completed	Healthy subjects or diagnosis of patients	Duration of treatment with sufentanil	Trial status; type of report
SECTION 5.3.1 REPORTS OF BIOPHARMACEUTIC STUDIES									
Section 5.3.1.1 Bioavailability study reports									
BA	ARX-C-006	5.3.1.1-1	Compare PK of sublingual tablet to IV sufentanil	Single-center, open-label, randomized, crossover	Sufentanil tablet 15 µg; single dose; sublingual Sufentanil 5 µg over 20 minutes; single dose; IV	12 enrolled; 12 completed	Healthy subjects	Single dose	Complete; Full
BA	MPS101	5.3.1.1-2	Single-dose PK of different routes of administration and in combination with triazolam	Single-center, open-label, randomized, crossover	Sufentanil 15 µg/ triazolam 200 µg tablet; single dose; sublingual Sufentanil 15 µg tablet; single dose; sublingual Sufentanil 15 µg tablet; single dose; buccal Sufentanil 15 µg tablet; single dose of 3 tablets; oral Sufentanil 5 µg over 20 minutes; single dose; IV + triazolam tablet 125 µg; single dose; oral	12 enrolled; 12 completed	Healthy subjects	Single dose	Complete; Full
Type of trial	**Trial identifier**	**Location of trial report**	**Objective(s) of the trial**	**Trial design and type of control**	**Test product(s); dosage regimen; route of administration**	**Number of subjects enrolled; completed**	**Healthy subjects or diagnosis of patients**	**Duration of treatment with sufentanil**	**Trial status; type of report**
BA	IAP102	5.3.1.1-3	Single-dose PK of different routes of administration	Single-center, open- label, randomized, 6-sequence, 4-treatment, 4-period, crossover	Sufentanil tablet 15 µg; single dose; sublingual Sufentanil tablet 15 µg; single dose; buccal Sufentanil tablet 15 µg; single dose; oral Sufentanil 15 µg over 1 minute; single dose; IV All subjects received naltrexone 50 mg	25 enrolled; 22 completed	Healthy subjects	Single dose	Complete; Full
Section 5.3.1.2 Comparative bioavailability and bioequivalence study reports									
Not applicable									
Section 5.3.1.3 In-vitro/in-vivo correlation study reports									
Not applicable									
Section 5.3.1.4 Reports of bioanalytical and analytical methods for human studies									
Bioassay method	PRALABIN-116587-B	5.3.1.4-1	Validation of a method for the determination of sufentanil in human plasma (final version dated 20 Jul 2012)			Method applied for IAP101, IAP102, IAP104			Method validation report
Bioassay method	PRALABIN-116587-B	5.3.1.4-2	Amendment No 1 to the method validation report PRALABIN-116587-B (final version dated 22 Aug 2012)			Method applied for IAP101, IAP102, IAP104			Method validation report
Bioassay method	PRALABIN-116587-B	5.3.1.4-3	Amendment No 2 to the method validation report PRALABIN-116587-B (final version dated 19 Apr 2013)			Method applied for IAP101, IAP102			Method validation report

Type of trial	Trial identifier	Location of trial report	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects enrolled; completed	Healthy subjects or diagnosis of patients	Duration of treatment with sufentanil	Trial status; type of report
SECTION 5.3.2 REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS									
Section 5.3.2.1 Plasma protein binding study reports									
Not applicable									
Section 5.3.2.2 Reports of hepatic metabolism and drug interaction studies									
Not applicable									
Section 5.3.2.3 Reports of studies using other human biomaterials									
Not applicable									
SECTION 5.3.3 REPORTS OF HUMAN PHARMACOKINETIC (PK) STUDIES									
Section 5.3.3.1 Healthy subject PK and initial tolerability study reports									
PK	ARX-F01-01	5.3.3.1-1	Single and repeat-dose PK of different doses	Single-center, open- label, sequential	**Part 1** Sufentanil 5 µg over 10 minutes; single dose; IV Sufentanil tablet 2.5, 5, and 10 µg; single dose; sublingual **Part 2** Sufentanil tablet 5 µg; every 10 minutes for 4 doses; sublingual **Part 3** Day 0 Sufentanil liquid 5 µg; single dose; sublingual or sufentanil 5 µg over 10 minutes; single dose; IV Day 1 Sufentanil tablet 10 µg; single dose; sublingual Day 2 Sufentanil tablet 10 µg; every 20 minutes for 4 doses; sublingual **Part 4** Day 4 Sufentanil 50 µg over 20 minutes; single dose; IV Day 7 Sufentanil tablet 80 µg; 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 trial	Trial identifier	Location of trial report	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects enrolled; completed	Healthy subjects or diagnosis of patients	Duration of treatment with sufentanil	Trial status; type of report
PK	IAP101	5.3.3.1-2	Single and repeat-dose PK	Single-center, open- label, fixed-sequence, crossover; no control	Sufentanil tablet 15 µg; single dose; sublingual Sufentanil tablet 15 µg; every 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
Section 5.3.3.2 Patient PK and initial tolerability study reports									
Not applicable									
Section 5.3.3.3 Intrinsic factor PK study reports									
Not applicable									

Type of trial	Trial identifier	Location of trial report	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects enrolled; completed	Healthy subjects or diagnosis of patients	Duration of treatment with sufentanil	Trial status; type of report
Section 5.3.3.4 Extrinsic factor PK study reports									
PK	IAP104	5.3.3.4-1	PK drug interaction (ketoconazole)	Single-center, open- label, 2- treatment, 2- period, fixed-sequence	Sufentanil tablet 15 µg; single dose; sublingual Sufentanil tablet 15 µg; single dose; sublingual + ketoconazole tablet 400 mg; once daily for 3 days; oral All subjects received naltrexone 50 mg.	19 enrolled; 18 completed	Healthy subjects	Single dose with and without multiple ketoconazole doses	Complete; Full
Section 5.3.3.5 Population PK study reports									
PopPK	001.1	5.3.3.5-1	Population PK analysis of SST	See ARX-C-001, IAP101, IAP102, IAP104, IAP309, IAP310, and IAP311					Complete; Full

Type of trial	Trial identifier	Location of trial report	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects enrolled; completed	Healthy subjects or diagnosis of patients	Duration of treatment with sufentanil	Trial status; type of report
SECTION 5.3.4 REPORTS OF HUMAN PHARMACOLOGY (PD) STUDIES									
Section 5.3.4.1 Healthy subject PD and PK/PD study reports									
PK/PD	ARX-C-002	5.3.4.1-1	PK/PD of sufentanil and/or triazolam tablet combinations and comparison to IV sufentanil	Single-center, single-dose, randomized, crossover, open-label on Day 1 and Day 2, double-blind on Day 3 to Day 5	**Open label:** Sufentanil 5 µg over 20 minutes; single dose; IV (Cohorts 1 and 2) Triazolam tablet 125 µg; single dose; oral (Cohorts 1 and 2) **Double-blind:** Sufentanil 10 µg/triazolam 200 µg tablet; single dose; sublingual (Cohorts 1 and 2) Sufentanil 15 µg/triazolam 200 µg tablet; single dose; sublingual (Cohort 1) Sufentanil 10 µg tablet; single dose; sublingual (Cohorts 1 and 2) Sufentanil 10 µg/ triazolam 100 µg tablet; single dose; sublingual (Cohort 2)	24 enrolled; 24 completed	Healthy subjects (2 cohorts: Cohort 1 = subjects 18-60 years of age; Cohort 2 = subjects 61-80 years of age)	Single dose	Complete; Full
Section 5.3.4.2 Patient PD and PK/PD study reports									
Not applicable									

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
ARX-C-001	7 sites/ USA	Phase II; Randomized, double-blind, placebo control	Sufentanil 5 µg; Sufentanil 10 µg; Sufentanil 15 µg; placebo	Efficacy and safety	5 µg: 25/11; 10 µg: 26/9; 15 µg: 24/13; Placebo: 26/7	Up to 12 hours	46.2/53.8; 62.9	Patients following knee replacement surgery	SPID-12
ARX-C-005	3 sites/ USA	Phase II; Randomized, double-blind, placebo control	Sufentanil 10 µg; Sufentanil 15 µg; placebo	Efficacy and safety	10 µg: 31/22; 15 µg: 32/25; Placebo:	Up to 12 hours	4.5/95.5; 46.2	Patients following open abdominal surgery	SPID-12

					31/9				
ARX-C-004	3 sites/ USA	Phase II; Open-label	Sufentanil 15 µg via NanoTab delivery system	Functionality of NanoTab delivery system, efficacy, safety	15 µg: 30/26	Up to 12 hours	33.3/66.7; 65.7	Patients following knee replacement surgery	Proportion of patients who successfully complete the study without any System failure.
IAP310	14 sites/ USA	Phase III; Randomized, double-blind, placebo control	Sufentanil 15 µg, placebo; via NanoTab delivery system	Efficacy and safety	15 µg: 119/78; Placebo: 59/27	Up to 72 hours	25.6/74.4; 55.2	Patients following open abdominal surgery	SPID-48
IAP311	34 sites/ USA	Phase III; Randomized, double-blind, placebo control	Sufentanil 15 µg, placebo; via NanoTab delivery system	Efficacy and safety	15 µg: 321/215; Placebo: 105/43	Up to 72 hours	39.4/60.6; 66.2	Patients following knee or hip replacement surgery	SPID-48
IAP309	25 sites/ USA	Phase III; Randomized, open-label, active control	Sufentanil 15 µg via NanoTab delivery system; IV PCA pump with Morphine Sulfate, 1 mg/ dose	Efficacy and safety	15 µg: 178/146; Morphine: 181/136	Up to 72 hours	35.3/64.7; 63.9	Patients following open abdominal surgery or knee or hip replacement surgery	Proportion of patients who responded “good” or “excellent” on the PGA of method of pain control over the 48-hour study period

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

PK of the sufentanil sublingual tablet (SST) has been studied in seven phase I trials.

Trials with the final formulation:

- IAP102 - single-dose bioavailability trial comparing intravenous sufentanil and SST administered sublingually, buccally, or swallowed.
- IAP101 - single- and multiple-dose (every 20 minutes for 40 doses) trial of SST dispensed from the SSTS.
- IAP104 - single-dose drug interaction trial with SST and oral administration of a cytochrome P450 (CYP) 3A4 inhibitor (ketoconazole).

Trials with an earlier formulation:

- ARX-C-006 - single-dose bioavailability trial comparing intravenous sufentanil to SST.
- MPS101 - single-dose trial comparing different routes of administration (sublingual, buccal, oral) and in combination with triazolam.
- ARX-C-002 - single-dose pharmacokinetics/pharmacodynamics of SST or sufentanil/triazolam tablets and comparison to intravenous sufentanil (comparison in younger and older subjects).

- ARX-F01-01 - single- and repeat-dose trial of various dosage strengths of SST (5, 10, 20, and 80 µg).

In addition, a population pharmacokinetic analysis was conducted to characterize the pharmacokinetic data for the SST, identify and quantify clinically relevant covariates on population-pharmacokinetic parameters, and characterize SST pharmacokinetic characteristics in relevant patient populations following single-dose administration and repeat-dosing.

Absorption

Systemic exposure of sufentanil following sublingual administration was greater after multiple-dose compared to single-dose. After the last of the multiple doses, C_{max} and AUC_{0-20} were statistically significantly higher compared to those after single-dose administration (by approximately 7-fold and 26-fold, respectively)

C_{max} observed after the 40th multiple dosing (240 pg/mL) was lower than that observed after a single IV dose of 15 µg (361 pg/mL). Median T_{max} occurred at 0.33 hours (20 minutes) after the last of the multiple doses, which was a decrease of about 0.5 hours compared to the T_{max} of 0.83 hours seen after a single dose.

The AUC_{0-20} of the last dose after multiple-dose treatment was statistically significantly lower by about 32.3% compared to AUC_{0-800} after single-dose treatment. This effect was considered clinically not relevant as the patients will administer on an as-needed basis.

Sublingual, buccal, and swallowed routes of administration resulted in significantly lower C_{max}, AUC_{0-t}, and AUC_{0-inf} values, and longer T_{max} compared to IV sufentanil.

Bioavailability

Relative bioavailability of sufentanil sublingual administration was 59% in study IAP102, which used the final formulation of the tablet. Bioavailability from sublingual and buccal (78%) routes was similar while it was poor when sufentanil was swallowed (9%).

Sublingual bioavailability in the other BA studies using earlier formulations (ARX-C-006, MPS101) was 57% and 51%, respectively.

Distribution

A summary of data from the scientific literature for *in vitro* and animal studies has been provided, complemented by llimited data collected in the studies performed by the Applicant. It is acceptable that this information is taken mainly from the literature since after sublingual absorption the distribution of sufentanil is expected to happen in the same way as after IV administration.

Elimination

Sufentanil is rapidly and extensively metabolized in the liver by cytochrome CYP3A4, into a large number of inactive metabolites that are excreted with urine and faeces.

Similar $CST_{½}$ values were observed following both single and repeated administration demonstrating that there is a predictable and consistent duration of action after multiple dosing of the sublingual tablet. The median $t_{½}$ values were similar for IV, sublingual, buccal, and oral treatments and ranged from 2.80 to 4.63 h with oral administration having the longest $t_{½}$. The half-life of sufentanil was longer in elderly patients and shorter after multiple dosing and with increasing weight of subjects.

The terminal half-life of sufentanil was poorly characterized because in the early studies, analytical sensitivity was relatively low and because of that, the terminal half-life was underestimated. In study ARX-C-006 the terminal half-life was only 2.22 hours but when the analytical sensitivity was improved, median $t_{½}$ increased to 12.6 hours (Study IAP101) and 5.28 hours (Study IAP102). Further investigation by the NCA methodology determined that the limit of quantification has an impact on the reported terminal half-life but only for single-dose administration (mean of 6 hours to 10 hours). Upon repeated dosing, the mean estimated terminal half-life was up to 18 hours. This was also confirmed by the newly established pop PK model based on Phase I data. For a typical subject, the terminal half-life was estimated to be 16.2 hours.

After the last dose of multiple-dose administration, a slower elimination phase, compared to that observed after single-dose administration, was exhibited. The apparent clearance was 78.1 L/hr after a single-dose, increasing to 111.9 L/hr after repeated doses, decreasing to 56.9 L/hr in elderly patients, and decreasing to 45.2 L/hr in patients taking ketoconazole. The apparent central volume was 67.7 L. The distribution clearance and peripheral volume were 77.5 L/hr and 2200 L respectively.

Pharmacokinetics of metabolites

PK of sufentanil metabolites has not been studied. This was accepted by the CHMP since these metabolites have no opioid effect.

Dose proportionality

Dose proportionality has been studied in a clinical trial conducted with the earlier formulation of sufentanil NanoTab. The results show linear pharmacokinetics between 2.5 and 80µg.

Pharmacokinetics in target population

Plasma sufentanil concentrations measured in patients show a considerable range of variation, matching the individual frequency of dosing. There were no statistically significant differences between patients < 65 years of age and ≥ 65 years of age or between patients with BMI < 30 kg/m^2 or ≥ 30 kg/m^2 and also between patients with or without impaired hepatic function or impaired renal function.

No differences with the PK in healthy subjects were observed.

Special populations

The Applicant provided results from a population PK analysis in healthy volunteers and in subjects with acute pain which was described by a 2-compartment model with first-order transmucosal absorption and a lag time. Inter-individual variability on pharmacokinetic parameters was large, as would be expected given the variability in dosing and sampling in the Phase II and Phase III trials.

Gender and race or concomitant administration of CYP3A4 substrates does not appear to influence PK parameters. Weight has a positively correlated influence on apparent clearance as well as distribution clearance. The expected peak-trough difference in various representative subjects (age, weight stratifications) was <13 pg/mL.

Age appears to influence pharmacokinetics of sufentanil to a certain extent. Bioavailability was higher in elderly subjects (93-96% compared to 76–87% in younger subjects). Mean $t_{½}$ for sufentanil was slightly longer in older subjects, as well clearance, resulting in an increase of AUC_{0-t} and AUC_{0-inf}.

No dedicated studies in patients with renal or hepatic impairment were conducted, but experience with sufentanil and population PK analyses in the phase III studies indicate that clearance is not affected by these conditions. In the population pharmacokinetic analysis for Zalviso including 700 patients and healthy volunteers, neither renal nor hepatic function was identified as a significant covariate for clearance.

No studies in paediatric patients have been performed with the SST.

Interactions

Ketoconazole, a potent CYP3A4 inhibitor, can increase the systemic exposure to sufentanil. The healthy volunteers study to assess this interaction showed that AUC ($AUC_{0-\infty}$ 126.47 vs. 223.63), $t_{½}$ (0.87 vs. 1.27 h) and T_{max} (6.35 vs. 13.61 h) of sufentanil were significantly increased when given together with ketoconazole. This has been adequately reflected in the SmPC and it is not expected to cause clinical problems. With increased AUC, the duration of pain relief will be prolonged, so the patient is expected to increase the intervals between SST doses.

Studies MPS101 and ARX-C-002 were conducted in combination with triazolam. No drug-drug interactions were observed in these studies.

Other possible interactions of sufentanil have been discussed in Clinical Safety section of this report.

2.4.3. Pharmacodynamics

Mechanism of action

Sufentanil is a synthetic, potent opioid with highly selective binding to μ-opioid receptors. 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. Sufentanil produces a dose related attenuation of catecholamine release, particularly norepinephrine.

Primary pharmacology

No patient PD or PK/PD studies have been performed by the Applicant because pharmacodynamics of sufentanil has been characterised for the reference product. A PK/PD study has been performed in healthy volunteers with the earlier formulation of the sufentanil NanoTab and showed an effect of sufentanil on production of sedation for diagnostic or therapeutic procedures.

Secondary pharmacology

No special assessments of secondary pharmacological effects have been performed in the clinical studies. However, it is known that sufentanil can cause a range of secondary effects, which can result in adverse events. Therefore, this topic is discussed in Clinical Safety section of this assessment report.

2.4.4. Discussion on clinical pharmacology

Sufentanil is a known active substance with known pharmacokinetic und pharmacodynamic properties. The main goal of the clinical pharmacology development of Zalviso was to characterise new sublingual route of administration. The performed trials sufficiently describe the pharmacokinetic and pharmacodynamic profile of sufentanil given sublingually and establish good acceptance and bioavailability of the sublingual tablet. The covariate effects and magnitude of the pharmacokinetic parameters were consistent with previous pharmacokinetic publications for intravenous sufentanil.

Changes in formulation were performed several times during the clinical development of Zalviso. However, they have been judged to be of minor importance since only three studies performed with the latest formulation were considered as main source of information. The older studies were considered as supportive. In addition, the CHMP was able to draw comparisons between studies with older and newer formulation of the SST despite the complexity of the data (older studies did not use the same dosage and used a different analytical assay with a lower sensitivity).

All studies with the final SST formulation used naltrexone as a blocking agent against the opioid actions of sufentanil. However, the impact of naltrexone on the PK of sufentanil was judged to be insignificant.

The effects of age and weight on sufentanil PK profile were not considered to be of concern, because with increased AUC, also the duration of pain relief will be prolonged. Since Zalviso is used as PCA, the patients are expected to be able to adjust the uptake of sufentanil on their own within the given margins (20 min time-out). Hence, a possible overdose in e.g. elderly and anorectic patients is not probable.

The terminal half-life has been explored by the CHMP as an important parameter in post-dose safety. In addition the CHMP noted that the relatively slow, prolonged elimination profile observed after repeated administration might result in safety issues if the patient is discharged from a hospital without additional warnings. For example, car driving could be dangerous until sufentanil is completely eliminated from the body. Therefore, section 4.7 was updated accordingly to state that sufficient time should elapse before patients can drive or operate machinery.

Sufentanil, being a drug with high extraction ratio, is expected to be subject to reduced hepatic clearance if haemodynamic changes are present that reduce the blood flow through the liver. In the Phase III studies only 13 and 6 subjects had moderate and severe hepatic impairment, respectively. Therefore, it is likely that a hepatic dysfunction covariate was not detected due to the sparse data.

No special population studies were performed, but in an analysis of the population PK data neither renal nor hepatic function was identified as a significant covariate for clearance. However, due to the limited number of patients with severe renal impairment and moderate to severe hepatic impairment studied, it is recommended that Zalviso should be used with caution in such patients. This has been adequately reflected in the PI.

The influence of food on the absorption of SST has not been studied since absorption of sufentanil takes place sublingually and is therefore independent of the presence of food in the gastrointestinal tract. The CHMP endorsed the recommendation in the SmPC that eating and drinking should be prohibited for ten minutes after the administration of SST to minimize the risk of swallowing the SST.

Interaction with other sublingually administered products or products intended to dilute/establish an effect in the oral cavity were not evaluated. Therefore, the CHMP advised that simultaneous administration of such products should be avoided and the SmPC was updated accordingly. The CHMP also noted that the Applicant did not investigate the effects of factors which are able to change the pH or the temperature of the saliva, e.g. potential interaction with hot, cold or carbonated drinks. A sublingual absorption model was developed to explore the potential effects of temperature or changes in pH on the

resulting plasma concentration-time profile of sufentanil. It appears that the dissolution of the sufentanil microtablet is not the rate determining step, but rather the uptake of sufentanil from the sublingual depot controls the overall rate of absorption. Therefore, the CHMP concluded that additional warning regarding hot and cold beverage consumption is not needed in the SmPC.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered that the available clinical pharmacology data were suitable to support the Application for a marketing authorisation of Zalviso. The product information adequately reflects relevant pharmacology data, including the recommendation to administer Zalviso without food or drink.

2.4.6. Clinical efficacy

Dose-finding studies

The selection of 15 µg as the dose used in the pivotal clinical studies was based on two dose-finding clinical trials.

ARX-C-001 was a prospective, randomized, double-blind multicentre trial in patients 45 to 80 years of age who were undergoing elective knee replacement. The primary objective of this trial was to evaluate the efficacy of 3 doses of SST (5 µg, 10 µg or 15 µg) in the management of moderate to severe acute post-operative pain compared to placebo.

The primary efficacy endpoint was the sum of the pain intensity differences at each evaluation time point compared to baseline over the 12-hour study duration (SPID-12). A selection of additional outcome measures was also collected as secondary efficacy endpoints.

There were statistically significant differences in LS mean SPID scores between the ARXF01 15 µg group and the placebo group at all time points from 15 min to 12 hours ($p=0.038$ to $p=0.007$), with higher scores in the ARX-F01 groups than in the placebo group. There were no statistically significant differences in LS mean SPID scores between the ARX-F01 5 µg or 10 µg groups and the placebo group at any time point.

The difference between the 3 different dose arms and placebo was most pronounced for the discontinuation due to inadequate analgesia and time to onset of pain relief. The 15 µg dose was favoured in all of the explored endpoints although difference to placebo did not reach statistical significance for some endpoints. The three different doses were only tested against placebo but not against each other. The difference between 5µg and placebo was negligible so it was considered reasonable to drop this lowest dose.

ARX-C-005 was a prospective, multicentre, randomized, double-blind trial in patients 18 to 80 years of age who were undergoing major upper or lower abdominal surgery. The primary objective of this study was to evaluate the efficacy of two doses (10 µg and 15 µg) of ARX-F01 Sublingual Sufentanil NanoTabs in the acute treatment of moderate to severe postoperative pain compared to placebo. The efficacy endpoints were the same as for study ARX-C-001.

There were statistically significant differences between the ARX-F01 groups and the placebo group for LS mean SPID scores at all time points from 3 to 12 hours in the 15 µg dose group ($p=0.007$ to $p<0.001$) and

from 4 to 12 hours in the 10 µg dose group (p=0.048 to p<0.001), with higher mean SPID scores in the ARX-F01 groups than in the placebo group.

There were statistically significant differences between each ARX-F01 group and the placebo group for the proportion of subjects who terminated from the study due to inadequate analgesia (p<0.001), with 21 (70.0%) patients in the placebo group terminated due to inadequate analgesia compared with 7 (24.1%) and 3 (10.3%) patients, respectively, in the ARX-F01 10 µg and 15 µg groups.

The two different dose arms of sufentanil were not formally tested against each other, however, there was a consistent trend towards numerically better results for the higher dose level and thus it was considered appropriate to carry the 15 µg dose forward to the phase III trials. The CHMP agreed with this selection.

Main clinical studies

The main support for efficacy of Zalviso was provided by two placebo controlled phase III trials and one phase III study controlled against an IV PCA with morphine sulfate.

Studies IAP310 and IAP311 are discussed together as their main difference lies in the type of surgery - open abdominal for IAP310 and hip or knee replacement for IAP311.

IAP310: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® PCA System / 15 µg for the Treatment of Post-Operative Pain in Patients after Open Abdominal Surgery

IAP311: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® PCA System / 15 µg for the Treatment of Post-Operative Pain in Patients after Knee or Hip Replacement Surgery

Methods

Study participants

Patients were included in the study if all of the following inclusion criteria were met at screening:

- Male or female age 18 or older;
- Patients classified as American Society of Anesthesiologists class I to III;
- For protocol IAP310 patients scheduled to undergo an open abdominal surgery (including laparoscopic-assisted) under general or spinal anaesthesia that did not include intrathecal opioids during the operation;
- For protocol IAP311 patients scheduled to undergo an open elective cemented or uncemented total unilateral knee replacement or total unilateral hip replacement under general or spinal anaesthesia that did not include intrathecal opioids during the operation;
- Post-surgical patients who had been admitted to the PACU and were expected to remain hospitalized and to have acute pain requiring parenteral opioids for at least 48 hours after surgery;
- Manual dexterity to handle the Nano Tab system;

Main exclusion criteria at screening were as follows:

- 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;

- Patients with a positive drug of abuse urine screen unless the positive test result was consistent with a prescribed medication;
- 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;
- Patients who had used any illicit drugs of abuse within 5 years before the start of the study;
- Patients who had abused any prescription medication or alcohol within 1 year before the start of the study;
- Patients with an allergy or hypersensitivity to opioids;
- Patients who were currently taking monoamine oxidase inhibitors (MAOIs) or had taken MAOIs within 14 days of the first dose of study drug;
- Patients with current sleep apnoea that had been documented by a sleep laboratory study or were on home continuous positive airway pressure
- Patients who received perioperative regional anaesthetic techniques including epidural, intra-articular, peripheral nerve block, and local anaesthetic wound infiltration;
- Patients who were expected to have post-operative analgesia supplied by a long acting continuous regional technique;
- Patients who received surgical premedication with long-acting opioid analgesics;
- Patients who were receiving oxygen therapy at the time of screening.

Patients with any of the following exclusion criteria at Randomization were excluded from the study:

- Patients who were not awake, not breathing spontaneously, or had a respiratory rate that was less than 8 bpm or greater than 24 bpm;
- Patients with arterial oxygen saturation by pulse oximetry (SpO2) that could not be maintained at ≥ 95% with or without supplemental oxygen;
- Patients not able to answer questions and follow commands;
- Patients who were vomiting and not responsive to standard treatment;
- Patients who had any deviation from the allowed surgical or anaesthetic protocols.

Treatments

Patients were randomly assigned to treatment with either Sufentanil NanoTab 15 µg PCA System or Placebo NanoTab PCA System.

The NanoTabs were to be dissolved under the tongue and were not to be crushed, chewed, or swallowed. Patients were instructed not to eat or drink, and to minimize talking for 10 minutes after a NanoTab had been administered, although ice chips could have been used to avoid excessively dry mouths in patients during the study period.

Objectives

The primary objective of these studies was to compare the efficacy and safety of the Sufentanil NanoTab PCA System to placebo in the management of acute post-operative pain after open abdominal surgery (IAP310)/ after total unilateral knee or total unilateral hip replacement surgery (IAP311).

Secondary objectives were to assess patient ratings of pain intensity and pain relief, percentage of patients requiring rescue due to inadequate analgesia, global assessments and questionnaires, and the use of IV supplemental and rescue opioid medication.

Outcomes/endpoints

The primary efficacy endpoint was the time-weighted summed pain intensity difference (SPID) over the 48-hour study period (SPID48). Pain intensity was measured using an 11-point NRS with 0 (no pain) and 10 (worst possible pain).

The secondary efficacy endpoints were:

1. Modified time-weighted SPID48 without including any pain intensity data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 48-hour study period

2. Time-weighted SPID over the 24-hour study period (SPID24) and time-weighted SPID over the 72 hour study period (SPID72)

3. Modified time-weighted SPID24 and modified time-weighted SPID72

4. Total pain relief (TOTPAR) over the 24-hour study period (TOTPAR24), the 48-hour study period (TOTPAR48), and the 72-hour study period (TOTPAR72)

5. Modified TOTPAR24, TOTPAR48, and TOTPAR72 without including any pain relief (PR) data collected after a patient received the first dose of rescue opioid in the calculation of these efficacy endpoints

6. Time-weighted summed pain relief intensity difference SPRID over 24-hour study period (SPRID24), the 48-hour study period (SPRID48) and the 72 hour study period (SPRID72)

7. Proportion of patients who terminated from the study due to inadequate analgesia over the 24-hour, 48-hour, and 72-hour study periods

8. Proportion of patients requiring rescue medication due to inadequate analgesia over the 24-hour, 48-hour, and 72-hour study periods

9. Total amount of supplemental and rescue morphine utilized over the 48-hour study period

10. Proportion of patients and healthcare professionals who responded to the global assessments as “excellent” or “good”

11. Proportion of patients and healthcare professionals who responded in each category of the global assessments

12. Patient and Nurse EOC Questionnaire data

13. Patient and Nurse System Questionnaire data and patient SUS data

14. Pain intensity and pain intensity difference (PID) at each evaluation time point

15. Pain relief (PR) and pain relief intensity difference (PRID) at each evaluation time point. The PRID is the sum of PR and PID

16. Total number of study drug doses used over 24, 48, and 72-hour study periods

17. Mean duration of inter-dosing interval over 24, 48, and 72-hour study periods

Sample size

IAP310

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 SPID48. This sample had 90% 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 a 2:1 sample size allocation ratio and a significance level of α=0.05. Assuming a 10% non-evaluable rate, 180 patients were planned to be randomized in this study.

IAP311

A sample size of 400 patients (300 sufentanil-treated patients and 100 placebo patients) was based on an effect size of 0.40 for the primary efficacy endpoint, time-weighted SPID48. This sample had 90% 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 a 3:1 sample size allocation ratio and a significance level of α=0.05. Assuming a 10% non-evaluable rate, 440 patients were planned to be randomized to this study.

Randomisation

Patients who were deemed eligible for study participation were randomized at a 2:1 allocation ratio (for study IAP310) or a 3:1 allocation ratio (for study IAP311) to receive Sufentanil NanoTab System or Placebo NanoTab System. Following surgery, the Interactive Web Response Systems (IWRS) was used to assign the treatment for each patient.

Blinding (masking)

Both trials were double blind. The study sponsor, the Investigator, other study centre personnel, and patients were blinded to treatment group assignment. Study drug for both treatments were identical in appearance.

Statistical methods

Analysis Populations

The main analysis of the primary and secondary efficacy endpoints was performed on the ITT population which included all randomized patients who received study medication. The Completers population included those ITT patients who completed the 48-hour study period per protocol. The primary and secondary efficacy variables for Completers were analysed. All randomized patients who received at least one dose of study drug were included in the safety analysis and summaries.

Statistical Analysis of the Primary Efficacy Variable

The primary efficacy endpoint was the time-weighted summed pain intensity difference (SPID) over the 48-hour study period (SPID48). Pain intensity was measured using an 11-point NRS with 0 (no pain) and 10 (worst possible pain) (see above).

The PID at each evaluation time point after the initiation of the first dose was the difference in pain intensity at the specific evaluation time point and baseline pain intensity [PID (evaluation time after the first dose) = pain intensity (baseline) – pain intensity (evaluation time after the first dose)]. The time-weighted SPID48 is the time-weighted summed PID over the 48-hour study period.

$$\text{Time-weighted SPID48} = \Sigma\,[T(i) - T(i-1)] \times PID(i),$$

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 48 hours

A parallel lines analysis of covariance (ANCOVA) model was used for the analysis of the primary efficacy endpoint. This ANCOVA model included treatment and center (as well as surgery type for IAP311) factors, and baseline pain intensity as a covariate. The least squares mean of each treatment and its 95% confidence interval (CI) were presented. The difference between the Sufentanil NanoTab System and the Placebo NanoTab System groups (Sufentanil NanoTab System minus Placebo NanoTab System) in the LS mean time-weighted SPID48 score and its 95% CI were constructed.

Missing Data

The study period consisted of a minimum of 48 hours and could extend up to 72 hours after the first on-demand dose of study drug. For patients missing pain intensity or PR data, the following methods were applied to impute the missing data at evaluation time points for the duration of 72-hour study period:

(1) Missing data were first imputed on a patient-by-patient basis by 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. The worst PID is the smaller number between number zero and the last PID obtained prior to termination. The worst PR is number zero.

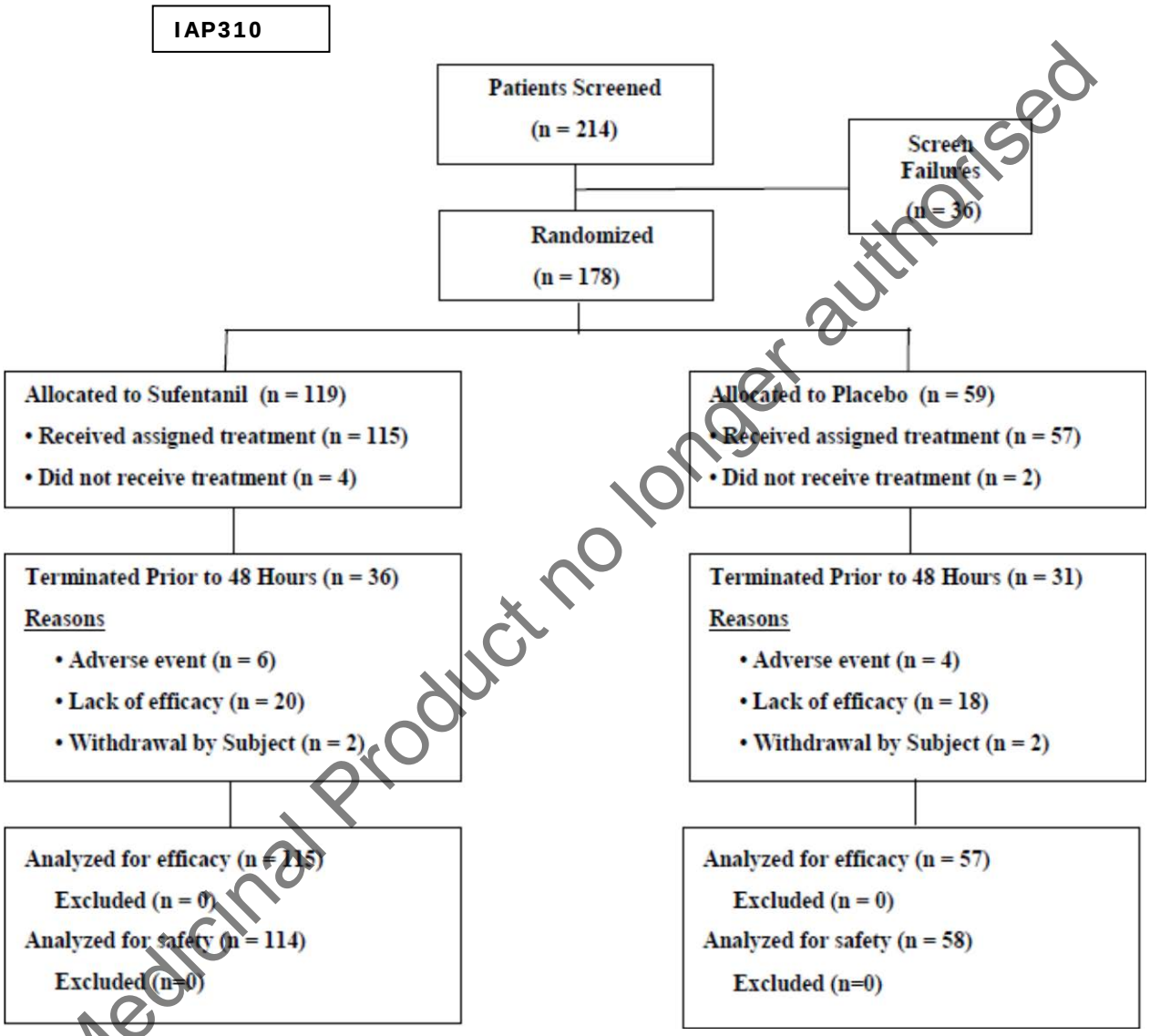
The pain intensity data collected after a patient received the first dose of rescue opioid were included in the calculation of the primary efficacy endpoint, time-weighted SPID48.

For patients who used any rescue or supplemental opioid during the study period, the last observed pain intensity prior to using each dose of rescue or supplemental opioid was carried throughout a follow-up 1-hour time interval. Any pain intensity collected within 1 hour after the start of any rescue or supplemental opioid was excluded from the calculation of the primary efficacy endpoint, time-weighted SPID48. This same imputation method was also used to calculate the secondary efficacy endpoints of time-weighted SPID24, time-weighted SPID72, and TOTPAR.

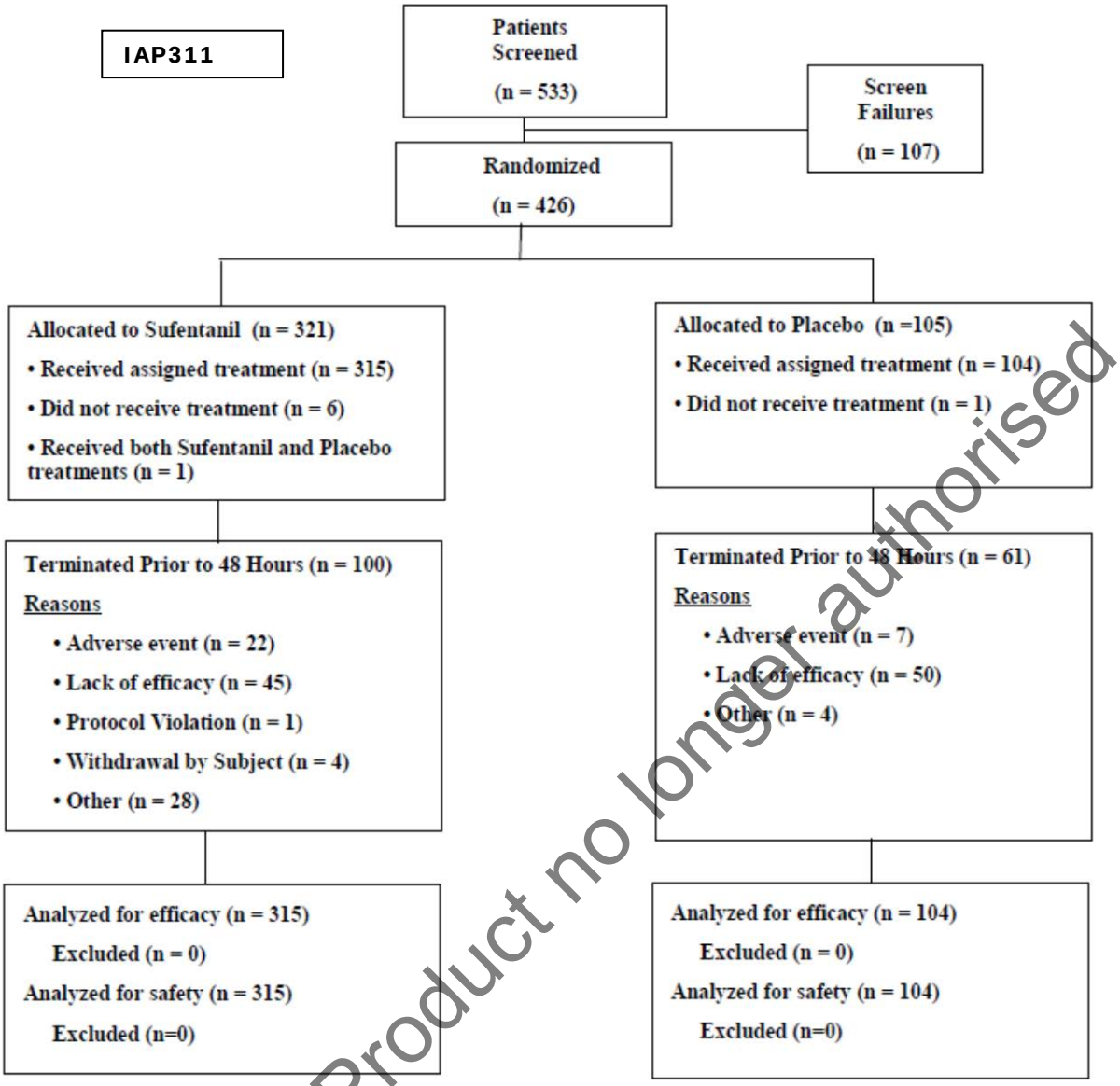
Sensitivity analyses using different imputation methods (LOCF, WOCF and baseline observation carried forward [BOCF]) were performed on the primary efficacy endpoint, time-weighted SPID48, to determine the effect of different methods of handling missing data on these endpoint calculations.

Results

Participant flow



Study Completers were allowed to continue in the study beyond 48 hours. A total of 52 patients chose to do so, and 40 of these patients completed the 72-hour study period. 29 of them were in the Sufentanil group and 11 in the placebo group.



Study Completers were allowed to continue in the study beyond 48 hours. A total of 150 patients chose to do so, and 85 of these patients (56.7%) completed the 72-hour study period. 69 of them were in the Sufentanil and 16 in the placebo group.

Recruitment

IAP310

Date first patient enrolled: 6 March 2012

Date last patient completed: 11 January 2013

IAP311

Date first patient enrolled: 22 August 2012

Date last patient completed: 07 April 2013

Conduct of the study

IAP310

There were six amendments to Protocol IAP310. Most amendments were minor and clarified inclusion or exclusion criteria. Amendment 6, dated 30 November 2012, made the following changes:

• Redefined the calculation of the primary efficacy endpoint (time-weighted SPID48).

• Redefined the calculation of the first secondary efficacy endpoint (modified time-weighted SPID48).

• Redefined the calculation of the following secondary efficacy endpoints: modified time-weighted SPID24 and SPID72, and modified TOTPAR.

IAP311

There was one amendment to Protocol IAP311, dated 27 July 2012, which made the following changes:

• Redefined the calculation of the primary efficacy endpoint, time-weighted summed pain intensity difference (SPID) over the 48-hour study period (SPID48).

• Redefined the calculation of the first secondary efficacy endpoint, modified time-weighted SPID48.

Protocol deviations occurred in both studies, and included patients randomized but not dosed, incorrect time settings, missed pain scores.

Baseline data

Tables 7 and 8 provide an overview of the demographics of the study populations.

Table 7 Demographics and baseline characteristics (ITT population)

	Sufentanil NanoTab System (n = 115)	Placebo NanoTab System (n = 57)	Total (n = 172)
Age (years)*			
< 65	92 (80.0%)	35 (61.4%)	127 (73.8%)
≥ 65	23 (20.0%)	22 (38.6%)	45 (26.2%)
Mean (SD)	54.2 (13.5)	57.4 (14.9)	55.2 (14.0)
Min, max	23.0, 92.0	31.0, 86.0	23.0, 92.0
Sex*			
Male	35 (30.4%)	9 (15.8%)	44 (25.6%)
Female	80 (69.6%)	48 (84.2%)	128 (74.4%)
Race			
White	78 (67.8%)	42 (73.7%)	120 (69.8%)
Black or African American	34 (29.6%)	15 (26.3%)	49 (28.5%)
Asian	2 (1.7%)	0	2 (1.2%)
Native American	1 (0.9%)	0	1 (0.6%)
Ethnicity			
Hispanic or Latino	8 (7.0%)	2 (3.5%)	10 (5.8%)
Not Hispanic or Latino	107 (93.0%)	55 (96.5%)	162 (94.2%)
Body Mass Index (kg/m^2)			
< 30	66 (57.4%)	31 (54.4%)	97 (56.4%)
≥ 30	49 (42.6%)	26 (45.6%)	75 (43.6%)
Mean (SD)	29.5 (6.8)	31.2 (8.2)	30.1 (7.3)
Min, max	18.0, 53.3	18.0, 52.0	18.0, 53.3

Source: Table 14.1.6.

SD: standard deviation; ITT: intent-to-treat; NanoTab System: Sufentanil NanoTab PCA System/15 mcg.

* Statistically significant difference between treatment groups from Fisher's exact test; age: p = 0.016; sex: p = 0.042.

Table 8 Demographics and baseline characteristics (ITT population)

	Sufentanil NanoTab System (n = 315)	Placebo NanoTab System (n = 104)	Total (n = 419)
Age (years)			
< 65	129 (41.0%)	50 (48.1%)	179 (42.7%)
≥ 65	186 (59.0%)	54 (51.9%)	240 (57.3%)
Mean (SD)	66.6 (10.8)	65.0 (10.5)	66.2 (10.7)
Min, max	26.0, 90.0	33.0, 87.0	26.0, 90.0
Sex			
Male	127 (40.3%)	38 (36.5%)	165 (39.4%)
Female	188 (59.7%)	66 (63.5%)	254 (60.6%)
Race			
White	277 (87.9%)	91 (87.5%)	368 (87.8%)
Black or African American	34 (10.8%)	12 (11.5%)	46 (11.0%)
Asian	2 (0.6%)	1 (1.0%)	3 (0.7%)
American Indian or Alaska Native	1 (0.3%)	0	1 (0.2%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0	1 (0.2%)
Ethnicity			
Hispanic or Latino	8 (2.5%)	1 (1.0%)	9 (2.1%)
Not Hispanic or Latino	307 (97.5%)	103 (99.0%)	410 (97.9%)
Body Mass Index (kg/m^2)			
< 30	170 (54.1%)	52 (50.5%)	222 (53.2%)
≥ 30	144 (45.9%)	51 (49.5%)	195 (46.8%)
Mean (SD)	30.5 (6.9)	31.0 (6.0)	30.6 (6.7)
Min, max	12.6, 62.0	20.0, 55.1	12.6, 62.0
Surgery			
Knee	152 (48.3%)	49 (47.1%)	201 (48.0%)
Hip	163 (51.7%)	55 (52.9%)	218 (52.0%)

Source: Table 14.1.6.
SD: standard deviation; ITT: intent-to-treat; Sufentanil NanoTab System: Sufentanil NanoTab PCA System/15 mcg.

The investigated patient population was comparable between the sufentanil and placebo arms. A substantial proportion of patients was aged ≥65. A wide range of body mass indexes was included (12.6 - 62). More female than male patients were enrolled in both studies, more pronouncedly so for IAP310.

Numbers analysed

A total of 178 patients were enrolled and randomized in study IAP 310; 6 patients did not receive study drug, leaving 172 patients who received study drug and were included in the ITT and safety populations. Of these 172 patients, 105 (61.0%) completed the 48-hour study period (Study Completers) and were included in the analysis of the primary efficacy endpoint for Completers.

A total of 426 patients were enrolled and randomized in study IAP311; 7 patients did not receive study drug, leaving 419 patients who received study drug and were included in the ITT and safety populations. Of these 419 patients, 258 (61.6%) completed the 48-hour study period (Study Completers) and were included in the analysis of the primary efficacy endpoint for Completers.

Outcomes and estimations

Primary endpoint analysis

Study IAP310

For the ITT population, there was a statistically significant difference between treatment groups for time-weighted SPID48 (p = 0.001), with higher mean SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (LS mean [SEM]: 105.60 [10.14] vs. 55.58 [13.11]).

There were also statistically significant differences between treatment groups for time-weighted SPID48 calculated using LOCF (p = 0.002), baseline observation carried forward (BOCF; p = 0.001), or WOCF (p = 0.001) imputation methods for missing post-termination pain intensity data, with higher mean SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all imputation methods.

Table 9 Analysis of Time-weighted SPID48: ITT Population

IAP310	Sufentanil NanoTab System (n = 115)	Placebo NanoTab System (n = 57)	P-value [1]
Baseline Pain Intensity			
Mean (SD)	5.87 (1.25)	6.09 (1.29)	
LS mean (SEM)	5.70 (0.11)	5.94 (0.15)	0.160
95% CI	(5.48, 5.92)	(5.65, 6.23)	
Time-weighted SPID48			
Mean (SD)	100.39 (96.71)	57.74 (107.97)	
LS mean (SEM)	105.60 (10.14)	55.58 (13.11)	0.001
95% CI	(85.58, 125.62)	(29.69, 81.48)	
Difference†			
LS mean (SEM)	50.02 (15.25)	NA	
95% CI	(19.89, 80.14)		

Source: Table 14.2.1.

†Sufentanil NanoTab System minus Placebo NanoTab System.

CI: confidence interval; ITT: intent-to-treat; LS: least squares; NA: not applicable; Sufentanil NanoTab System: Sufentanil NanoTab PCA System/15 mcg; SD: standard deviation; SEM: standard error of the LS mean; SPID48: summed pain intensity difference over the 48-hour study period.

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

For the time-weighted SPID48, the LS mean and SEM were estimated from the ANCOVA model that included treatment and center factors, and baseline pain intensity as a covariate.

[1] P-value for the test of treatment effect is based on Type III analysis from the models described above.

Study IAP311

For the ITT population, there was a statistically significant difference between treatment groups for time-weighted SPID48 (p < 0.001), with higher mean SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (LS mean [SEM]: 76.24 [7.02] vs. -11.35 [10.55]).

There were also statistically significant differences between treatment groups for time-weighted SPID48 calculated using either last observation carried forward (LOCF), baseline observation carried forward (BOCF), or worst observation carried forward (WOCF) ($p < 0.001$ for all) imputation methods for missing post-termination pain intensity data, with higher mean SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all imputation methods.

Table 10 Analysis of Time-weighted SPID48: ITT Population

IAP311	Sufentanil NanoTab System (n = 315)	Placebo NanoTab System (n = 104)	P-value [1]
Baseline Pain Intensity			
Mean (SD)	5.63 (1.08)	5.49 (0.89)	
LS mean (SEM)	5.57 (0.07)	5.43 (0.11)	0.215
95% CI	(5.43, 5.72)	(5.21, 5.65)	
Time-weighted SPID48			
Mean (SD)	77.17 (107.39)	-15.27 (120.52)	
LS mean (SEM)	76.24 (7.02)	-11.35 (10.55)	< 0.001
95% CI	(62.43, 90.05)	(-32.08, 9.38)	
Difference†			
LS mean (SEM)	87.59 (10.88)	NA	
95% CI	(66.20, 108.98)		

Source: Table 14.2.1.

† Sufentanil NanoTab System minus Placebo NanoTab System.

CI: confidence interval; ITT: intent-to-treat; LS: least squares; NA: not applicable; Sufentanil NanoTab System: Sufentanil NanoTab PCA System/15 mcg; SD: standard deviation; SEM: standard error of the LS mean; SPID48: summed pain intensity difference over the 48-hour study period.

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

For the time-weighted SPID48, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and surgery type factors, and baseline pain intensity as a covariate.

[1] P-value for the test of treatment effect is based on Type III analysis from the models described above.

Secondary endpoints

IAP310

Modified Time-weighted SPID48

There was a statistically significant difference between treatment groups for modified time-weighted SPID48 ($p < 0.001$), with higher mean modified SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group.

Time-weighted SPID24 and SPID72 and Modified Time-weighted SPID24 and SPID72

There were statistically significant differences between treatment groups for SPID24 ($p < 0.001$), SPID72 ($p = 0.004$), modified SPID24 ($p < 0.001$), and modified SPID72 ($p < 0.001$), with higher mean scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all variables.

Total Pain Relief (TOTPAR) and Modified TOTPAR

There were statistically significant differences between treatment groups for TOTPAR24 ($p < 0.001$), TOTPAR48 ($p = 0.002$), TOTPAR72 ($p = 0.004$), modified TOTPAR24 ($p < 0.001$), modified TOTPAR48 (p

< 0.001), and modified TOTPAR72 (p < 0.001), with higher mean scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all variables.

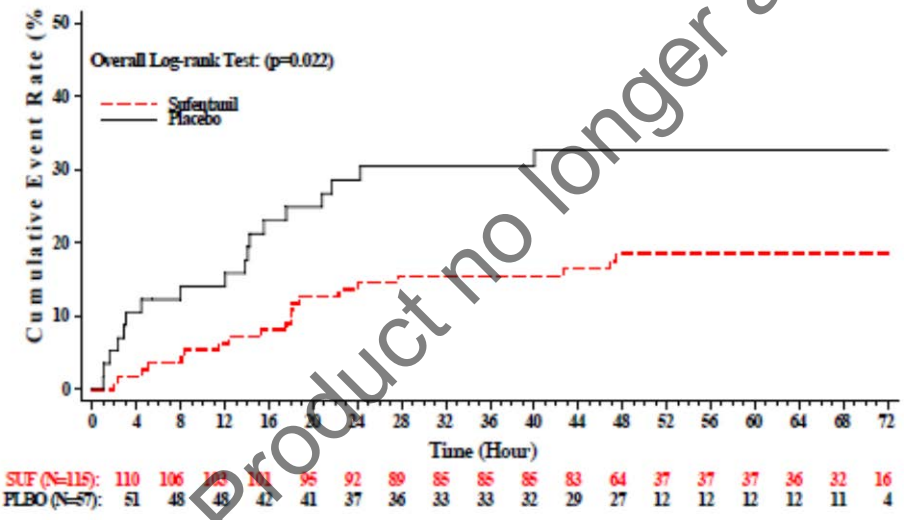
Time-weighted Summed Pain Relief Intensity Difference (SPRID)

There were statistically significant differences between treatment groups for SPRID24 (p < 0.001), SPRID48 (p = 0.001), and SPRID72 (p = 0.003), with higher mean scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all variables.

Terminations due to Inadequate Analgesia

A significantly greater proportion of patients in the Placebo NanoTab System group discontinued the study due to inadequate analgesia than in the Sufentanil NanoTab System group (18/57, 31.6% vs. 20/115, 17.4%; p = 0.035). There was also a statistically significant difference between treatment groups for time to discontinuation due to inadequate analgesia (p = 0.022), with patients in the Placebo NanoTab System group discontinuing earlier than in the Sufentanil NanoTab System group.

Figure 4: Kaplan-Meier Cumulative Event Rates for Time to Termination from the Study Due to Inadequate Analgesia: ITT Population



Source: Figure 14.2.12

ITT: intent-to-treat; PLBO/Placebo: Placebo NanoTab System; SUF/Sufentanil: Sufentanil NanoTab PCA System/95 mcg

P-value based on the log-rank test between treatment groups.

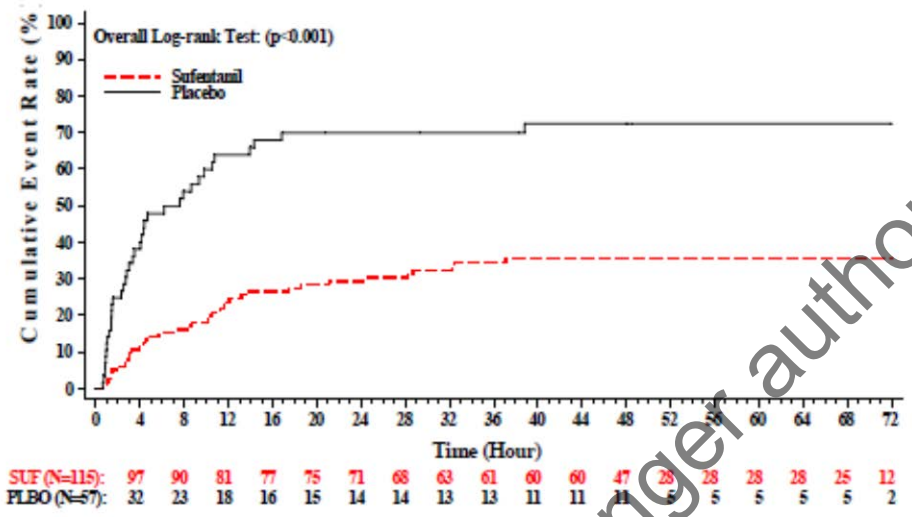
Rescue and Supplemental Medication Use

A significantly higher proportion of patients in the Placebo NanoTab System group (38/57, 66.7%) required rescue medication due to inadequate analgesia than in the Sufentanil NanoTab System group (38/115, 33.0%; p < 0.001). Additionally, the time to take the first rescue medication due to inadequate analgesia was also significantly longer in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (p <0.001).

There were no significant differences between treatment groups for supplemental morphine use during the first 30 minutes of the study. For the cumulative amount of rescue plus supplemental morphine used, there were significant differences between treatment groups for the proportion of patients requiring morphine during the first 6, 12, 18, 24, and 48 hours, with a smaller proportion of patients in the

Sufentanil NanoTab System group requiring morphine than in the Placebo NanoTab System group at all times ($p < 0.001$ for all). Additionally, the mean cumulative number of doses of morphine used at 6, 12, 18, 24, and 48 hours was significantly lower in the Sufentanil NanoTab System group than in the Placebo NanoTab System group ($p < 0.01$ for all).

Figure 5: Kaplan-Meier Cumulative Event Rates for Time to Take First Rescue Medication due to Inadequate Analgesia Over the 48-Hour Study Period: ITT Population



Source: Figure 14.2.14.
ITT: intent-to-treat; PLBO/Placebo: Placebo NanoTab System; SUF/Sufentanil: Sufentanil NanoTab PCA System/15 mcg
P-value based on the log-rank test between treatment groups.

Patient Global Assessment (PGA) and Healthcare Professional Global Assessment (HPGA) of Method of Pain Control

There were statistically significant differences between treatment groups for patient responses on the PGA and healthcare professional responses on the HPGA at 24, 48, and 72 hours ($p < 0.05$ for all). More patients and more healthcare professionals reported Success (i.e., responded good or excellent) on the PGA and HPGA, respectively, for the Sufentanil NanoTab System group than for the Placebo NanoTab System group at all times.

Patient and Nurse Ease-of-Care (EOC) Questionnaire Results

For Patient EOC Questionnaire scores, there were no statistically significant differences between treatment groups for any of the subscale scores or the total EOC score. The only exception was for the mean pain control score, which was significantly higher (better) in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (3.46 vs. 2.87; $p = 0.011$). The mean total score (out of a maximum of 5) was 4.39 in the Sufentanil NanoTab System group and 4.36 in the Placebo NanoTab System group. There was a statistically significant difference between treatment groups for patient satisfaction with level of pain control ($p = 0.011$), with a higher proportion of patients in the Sufentanil NanoTab System group being very satisfied with the level of pain control than in the Placebo NanoTab group.

For the Nurse EOC Questionnaire, there were no statistically significant differences between treatment groups for either of the subscale scores, the total EOC score, or either of the satisfaction scores.

The similar results for Patient and Nurse EOC scores were expected because most questions related to ease of use of the device and the NanoTab System device was the same for both treatment groups.

Patient System Questionnaire and System Usability Scale (SUS) Results

There were no statistically significant differences between treatment groups for responses on the Patient System Questionnaire or the SUS. Between 97.3% and 100% of patients in the Sufentanil NanoTab System group and 96.2% and 100% of patient in the Placebo NanoTab System group responded “yes” to each of the questions on the Patient System Questionnaire, indicating that they found the NanoTab System easy and convenient to use. The mean (SD) SUS score (out of a maximum of 100) was 87.1 (14.6) in the Sufentanil NanoTab System group and 86.1 (14.0) in the Placebo NanoTab System group. These results were expected since the NanoTab System was the same for both treatment groups.

Pain Intensity, Pain Intensity Difference (PID), Pain Relief, and Pain Relief Intensity Difference (PRID) by Evaluation Timepoint

There were statistically significant differences between treatment groups for pain intensity, PID, pain relief, and PRID scores at multiple timepoints during the study, with more favorable scores observed in the Sufentanil NanoTab System group than in the Placebo NanoTab System group at all times.

Study Drug Dosing over 24, 48, and 72 hours and Inter-dosing Interval

The mean inter-dosing interval was significantly longer in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (100 vs. 79 min; $p = 0.044$). However, there were no statistically significant differences between treatment groups for the total number of doses of study drug used or the number of doses used by study period.

IAP311

Modified Time-weighted SPID48

There was a statistically significant difference between treatment groups for modified time-weighted SPID48 ($p < 0.001$), with higher mean modified SPID48 scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group.

Time-weighted SPID24 and SPID72 and Modified Time-weighted SPID24 and SPID72

There were statistically significant differences between treatment groups for SPID24, SPID72, modified SPID24, and modified SPID72 ($p < 0.001$ for all), with higher mean scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all variables. In addition, significantly higher time-weighted SPID scores were observed in the Sufentanil NanoTab System group at all evaluation times from 2 to 72 hours.

Total Pain Relief (TOTPAR) and Modified TOTPAR

There were statistically significant differences between treatment groups for TOTPAR24, TOTPAR48, TOTPAR72, modified TOTPAR24, modified TOTPAR48, and modified TOTPAR72 ($p < 0.001$ for all), with higher mean scores in the Sufentanil NanoTab System group than in the Placebo NanoTab System group for all variables. In addition, significantly higher TOTPAR scores were observed in the Sufentanil NanoTab System group at all evaluation times from 2 to 72 hours.

Time-weighted Summed Pain Relief Intensity Difference (SPRID)

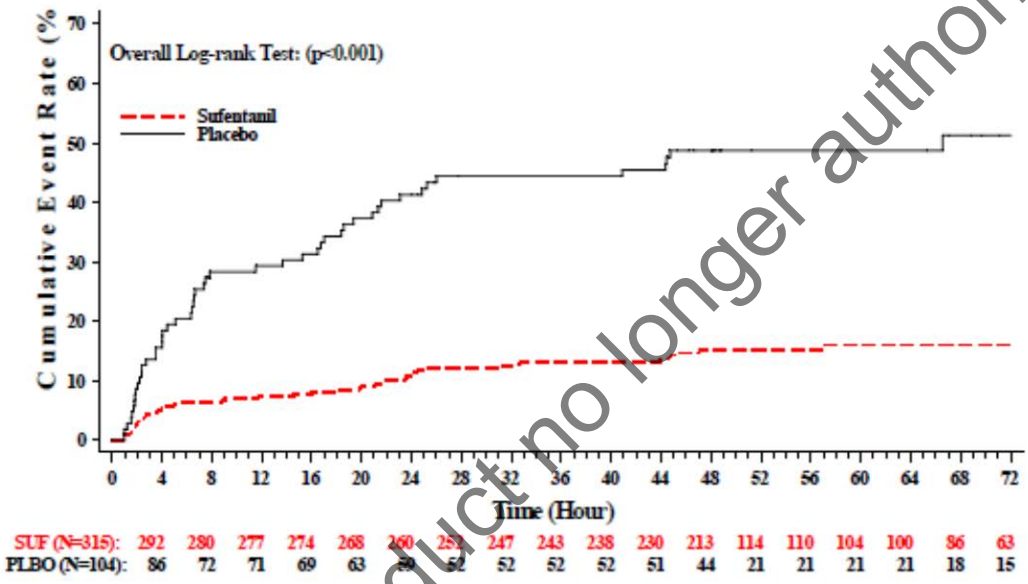
There were statistically significant differences between treatment groups for SPRID24, SPRID48, and SPRID72 ($p < 0.001$ for all), with higher mean scores in the Sufentanil NanoTab System group than in the

Placebo NanoTab System group for all variables. In addition, significantly higher time-weighted SPRID scores were observed in the Sufentanil NanoTab System group at all evaluation times from 2 to 72 hours.

Terminations due to Inadequate Analgesia

A significantly greater proportion of patients in the Placebo NanoTab System group discontinued the study due to inadequate analgesia than in the Sufentanil NanoTab System group (50/104, 48.1% vs. 45/315, 14.3%; p < 0.001). There was also a statistically significant difference between treatment groups for time to discontinuation due to inadequate analgesia (p < 0.001), with patients in the Placebo NanoTab System group discontinuing earlier than in the Sufentanil NanoTab System group.

Figure 4: Kaplan-Meier Cumulative Event Rates for Time to Termination from the Study Due to Inadequate Analgesia: ITT Population



Source: Figure 14.2.12.
ITT: intent-to-treat; PLBO/Placebo: Placebo NanoTab System; SUF/Sufentanil: Sufentanil NanoTab PCA System/15 mcg
P-value based on the log-rank test between treatment groups.

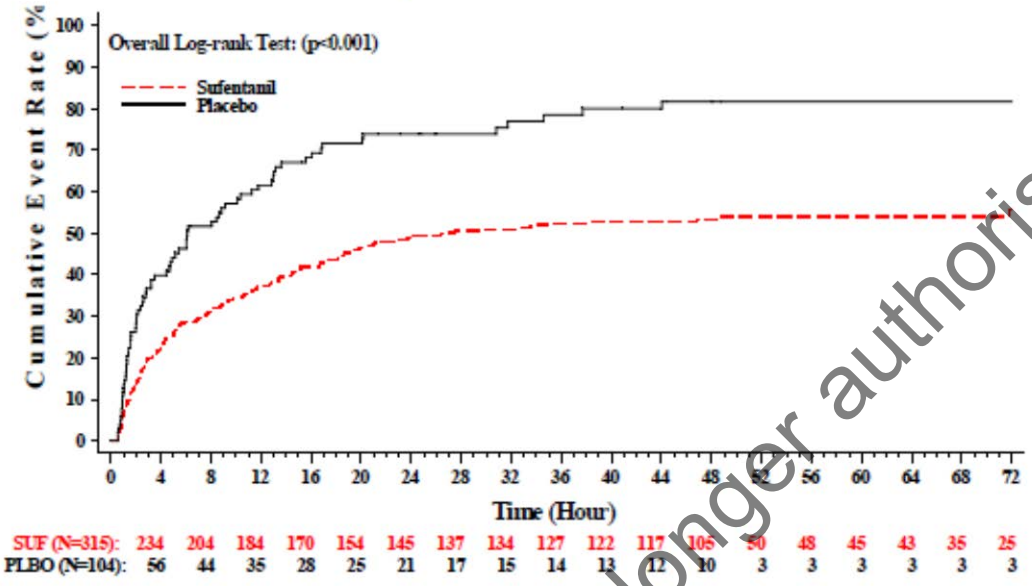
Rescue and Supplemental Medication Use

A significantly higher proportion of patients in the Placebo NanoTab System group (76/104, 73.1%) required rescue medication due to inadequate analgesia than in the Sufentanil NanoTab System group (160/315, 50.8%; p < 0.001). Additionally, the time to take the first rescue medication due to inadequate analgesia was also significantly longer in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (p <0.001). The median time to take the first rescue medication was 1590 minutes for the Sufentanil NanoTab System group compared to 366 minutes for the Placebo NanoTab System group.

For the cumulative amount of rescue plus supplemental morphine used, there were significant differences between treatment groups for the proportion of patients requiring morphine during the first 6, 12, 18, 24, and 48 hours, with a smaller proportion of patients in the Sufentanil NanoTab System group requiring morphine than in the Placebo NanoTab System group at all times (p = 0.002 at 6 hours; p < 0.001 for all other times). Additionally, the mean cumulative number of doses of rescue and supplemental morphine

used by 6, 12, 18, 24, and 48 hours was significantly lower in the Sufentanil NanoTab System group than in the Placebo NanoTab System group ($p < 0.001$ for all).

Figure 5: Kaplan-Meier Cumulative Event Rates for Time to Take First Rescue Medication due to Inadequate Analgesia Over the 48-Hour Study Period: ITT Population



Source: Figure 14.2.14.
ITT: intent-to-treat; PLBO/Placebo: Placebo NanoTab System; SUF/Sufentanil: Sufentanil NanoTab PCA System/15 mcg
P-value based on the log-rank test between treatment groups.

Patient Global Assessment (PGA) and Healthcare Professional Global Assessment (HPGA) of Method of Pain Control

There were statistically significant differences between treatment groups for patient responses on the PGA and healthcare professional responses on the HPGA at 24, 48, and 72 hours ($p < 0.001$ for all). More patients and more healthcare professionals reported Success (i.e., responded good or excellent) on the PGA and HPGA ratings of method of pain control, respectively, for the Sufentanil NanoTab System group than for the Placebo NanoTab System group at all times.

Patient and Nurse Ease-of-Care (EOC) Questionnaire Results

For Patient EOC Questionnaire scores, there were no statistically significant differences between treatment groups for any of the subscale scores or the total EOC score (mean total score: 4.39 and 4.29 [out of a maximum of 5] in the Sufentanil and Placebo NanoTab System groups, respectively). The only exception was for the mean pain control score, which was significantly higher (better) in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (3.44 vs. 2.72; $p < 0.001$). There was a statistically significant difference between treatment groups for patient satisfaction with level of pain control ($p < 0.001$), with a higher proportion of patients in the Sufentanil NanoTab System group being very satisfied or extremely satisfied with the level of pain control than in the Placebo NanoTab group.

For the Nurse EOC Questionnaire, there were no statistically significant differences between groups based on the nurses' length of experience with IV PCA systems for either of the subscale scores, the total EOC score, or the overall satisfaction score. However, the total satisfaction score was significantly higher

among nurses with > 1 year's experience with IV PCA than among those with ≤ 1 year's experience (4.07 vs. 3.65; p = 0.043).

The similar results for Patient and Nurse EOC scores were expected because most questions related to ease of use of the device and the NanoTab System was the same for both treatment groups.

Patient System Questionnaire and System Usability Scale (SUS) Results

There were no statistically significant differences between treatment groups for responses on the Patient System Questionnaire or SUS Questionnaire. Between 95.3% and 99.0% of patients in the Sufentanil NanoTab System group and between 96.6% and 100% of patients in the Placebo NanoTab System group responded "yes" to each of the questions on the Patient System Questionnaire, indicating that they found the NanoTab System easy and convenient to use. The mean (SD) SUS score (out of a maximum of 100) was 86.9 (14.24) in the Sufentanil NanoTab System group and 87.0 (15.11) in the Placebo NanoTab System group. These results were expected since the NanoTab System was the same for both treatment groups.

Pain Intensity, Pain Intensity Difference (PID), Pain Relief, and Pain Relief Intensity Difference (PRID) by Evaluation Time Point

There were statistically significant differences between treatment groups for pain intensity, PID, pain relief, and PRID scores at most time points during the study, with more favorable scores observed in the Sufentanil NanoTab System group than in the Placebo NanoTab System group at all times.

Study Drug Dosing over 24, 48, and 72 hours and Inter-dosing Interval

There were statistically significant differences between treatment groups for the total number of doses of study drug used and the number of doses used by study period, with a higher mean number of doses used in the Sufentanil NanoTab System group than in the Placebo NanoTab System group from 12 to 24 hours (p = 0.031), 24 to 48 hours (p = 0.001), 0 to 48 hours (p = 0.044), and for the total number of doses used over the 72-hour study period (p = 0.041). However, the LS mean interdosing interval was significantly longer in the Sufentanil NanoTab System group than in the Placebo NanoTab System group (83.5 vs. 57.8 min; p < 0.001). This longer inter-dosing interval in the Sufentanil NanoTab System group was likely because more patients in this group stayed in the study until 48 hours and the mean number of doses used from 24 to 48 hours (12 and 8 in the Sufentanil and Placebo NanoTab System groups, respectively) was lower than from 0 to 24 hours (22 and 21, respectively).

Ancillary analyses

The results of the primary endpoint analysis by demographic variables and BMI are presented in the Tables 11 and 12 below. There was a clear trend towards increased SPID48 scores for patients with a lower BMI, which is explainable by the fixed dose administered. Females showed slightly higher SPID48 scores than males, which could be explained by the higher average bodyweight of males.

Table 11 Analysis of Time-weighted SPID-48 Scores by Demographic Variables and BMI: IAP310 ITT population

Time-weighted SPID48	Sufentanil NanoTab System	Placebo NanoTab System	Difference[†]	P-value [1]
Age < 65 Yrs: n	92	35		
Mean (SD)	95.07 (94.79)	40.41 (105.31)		
LS mean (SEM)	96.40 (9.73)	36.91 (15.79)	59.50 (18.57)	0.002
95% CI	(77.15, 115.66)	(5.65, 68.17)	(22.74, 96.25)	
Age ≥ 65 Yrs: n	23	22		
Mean (SD)	121.68 (103.47)	85.32 (108.79)		
LS mean (SEM)	122.70 (21.56)	84.25 (22.04)	38.44 (30.84)	0.220
95% CI	(79.19, 166.20)	(39.77, 128.74)	(-23.80, 100.68)	
Male Patients: n	35	9		
Mean (SD)	95.70 (123.58)	109.74 (110.54)		
LS mean (SEM)	94.75 (20.35)	113.40 (40.20)	-18.65 (45.11)	0.681
95% CI	(53.66, 135.85)	(32.21, 194.60)	(-109.75, 72.45)	
Female Patients: n	80	48		
Mean (SD)	102.45 (83.12)	47.99 (105.81)		
LS mean (SEM)	106.12 (9.62)	41.88 (12.45)	64.24 (15.80)	< 0.001
95% CI	(87.08, 125.16)	(17.24, 66.52)	(32.96, 95.52)	
White Patients: n	70	40		
Mean (SD)	98.63 (97.09)	52.47 (104.76)		
LS mean (SEM)	101.83 (11.10)	46.88 (14.71)	54.95 (18.48)	0.004
95% CI	(79.82, 123.84)	(17.71, 76.04)	(18.31, 91.59)	
Non-White Patients: n	45	17		
Mean (SD)	103.14 (97.14)	70.15 (117.57)		
LS mean (SEM)	103.55 (15.22)	69.06 (24.78)	34.49 (29.09)	0.241
95% CI	(73.08, 134.01)	(19.48, 118.64)	(-23.72, 92.69)	
BMI< 30 kg/m^2: n	66	31		
Mean (SD)	91.95 (100.59)	56.78 (96.49)		
LS mean (SEM)	93.39 (11.79)	53.72 (17.22)	39.67 (20.89)	0.061
95% CI	(69.98, 116.80)	(19.53, 87.91)	(-1.82, 81.16)	
BMI ≥ 30 kg/m^2: n	49	26		
Mean (SD)	111.77 (91.01)	58.89 (122.23)		
LS mean (SEM)	113.87 (13.97)	54.93 (19.20)	58.94 (23.78)	0.016
95% CI	(86.02, 141.71)	(16.66, 93.20)	(11.53, 106.34)	

Table 12 Analysis of Time-weighted SPID-48 Scores by Demographic Variables and BMI: IAP311 ITT population

Time-weighted SPID48	Sufentanil NanoTab System	Placebo NanoTab System	Difference[†]	P-value [1]
Age < 65 Yrs: n	129	50		
Mean (SD)	68.75 (106.92)	-7.09 (116.73)		
LS mean (SEM)	57.00 (9.26)	-7.71 (14.41)	64.70 (17.04)	< 0.001
95% CI	(38.71, 75.28)	(-36.15, 20.74)	(31.06, 98.34)	
Age ≥ 65 Yrs: n	186	54		
Mean (SD)	83.01 (107.62)	-22.85 (124.53)		
LS mean (SEM)	87.50 (6.74)	-17.44 (12.43)	104.95 (14.15)	< 0.001
95% CI	(74.22, 100.79)	(-41.93, 7.05)	(77.06, 132.83)	
Male Patients: n	127	38		
Mean (SD)	91.15 (94.49)	-28.88 (120.00)		
LS mean (SEM)	84.43 (8.59)	-26.91 (15.47)	111.34 (17.68)	< 0.001
95% CI	(67.46, 101.40)	(-57.45, 3.64)	(76.43, 146.25)	
Female Patients: n	188	66		
Mean (SD)	67.72 (114.58)	-7.44 (121.03)		
LS mean (SEM)	69.61 (7.06)	-4.82 (11.91)	74.43 (13.86)	< 0.001
95% CI	(55.70, 83.52)	(-28.27, 18.62)	(47.12, 101.73)	
Caucasian Patients: n	269	90		
Mean (SD)	78.23 (109.78)	-9.72 (122.99)		
LS mean (SEM)	73.33 (5.93)	-12.51 (10.25)	85.84 (11.82)	< 0.001
95% CI	(61.67, 85.00)	(-32.66, 7.65)	(62.60, 109.09)	
Non-Caucasian Patients: n	46	14		
Mean (SD)	71.00 (93.03)	-50.96 (99.66)		
LS mean (SEM)	71.56 (14.42)	-38.15 (26.14)	109.71 (29.40)	< 0.001
95% CI	(42.68, 100.44)	(-90.51, 14.21)	(50.82, 168.60)	
BMI< 30 kg/m^2: n	170	52		
Mean (SD)	88.43 (110.97)	-20.09 (125.93)		
LS mean (SEM)	77.65 (7.72)	-31.74 (13.75)	109.39 (15.58)	< 0.001
95% CI	(62.43, 92.88)	(-58.84, -4.63)	(78.69, 140.09)	
BMI ≥ 30 kg/m^2: n	144	51		
Mean (SD)	64.25 (102.14)	-7.92 (115.56)		
LS mean (SEM)	68.06 (8.05)	4.64 (13.43)	63.42 (15.60)	< 0.001
95% CI	(52.18, 83.95)	(-21.85, 31.13)	(32.65, 94.19)	

IAP309

A Multicentre, Randomized, Open-Label, Parallel-Group Trial to Compare the Efficacy and Safety of the Sufentanil NanoTab® PCA System/15 µg to Intravenous Patient-Controlled Analgesia with Morphine for the Treatment of Acute Post-Operative Pain

Methods

Study participants

Inclusion and exclusion criteria were the same as for trials IAP310 and IAP311 with the difference that patients with open abdominal surgery as well as hip or knee replacement surgery were eligible.

Treatments

The patients were assigned to either Sufentanil NanoTab PCA System/15 µg or IV PCA pump with Morphine Sulfate, 1 mg/dose

Each study site used their standard IV PCA pump and followed standard institution procedures for use. The IV PCA pump was programmed to deliver MS 1 mg/dose with a 6-minute lockout interval. Basal infusion rates were not allowed.

Objectives

The primary objective of this study was to demonstrate the non-inferiority of the Sufentanil NanoTab System to IV PCA morphine sulfate (IV PCA MS) for the management of acute post-operative pain after major abdominal or orthopedic surgery.

Secondary objectives were to assess patient ratings of pain intensity and pain relief, percentage of patients dropping out due to inadequate analgesia, healthcare professional global assessment (HPGA) of method of pain control, use of IV opioid supplemental medication, patient and nurse Ease of Care (EOC) questionnaires, system-related events (SREs), interdosing intervals, and the safety of the NanoTab System in comparison to IV PCA MS.

Endpoints

The primary efficacy endpoint was the proportion of patients who responded “good” or “excellent” on the PGA of method of pain control over the 48-hour study period. The specific PGA question was: “Overall, how would you rate the method of pain control?”

The secondary efficacy variables were:

1. Proportion of patients who rated the PGA over 24 and 72 hours as “good” or “excellent”.

2. Proportion of patients who responded in each category of the PGA.

3. Proportion of healthcare professionals who rated the HPGA over 24, 48, and 72 hours as “good” or “excellent”.

4. Proportion of patients who terminated from the study due to inadequate analgesia over the 24-hour, 48-hour, and 72-hour study periods.

5. Time-weighted SPID24, SPID48, and SPID72

6. TOTPAR24, TOTPAR48, and TOTPAR72

7. Pain intensity at each evaluation time point

8. PID at each evaluation time point

9. PR at each evaluation time point.

10. PRID at each evaluation time point.

11. Time-weighted summed RASS scores over 24, 48, and 72 hours

12. Total number of study drug doses used over the 24-hour, 48-hour, and 72-hour study periods, average hourly use, and average inter-dosing interval.

13. Total amount of supplemental morphine utilized

14. Number of SREs

15. Patient and nurse EOC Questionnaires responses.

Sample size

Assuming a success rate of 75% for both treatment groups, a sample size of 352 patients (176 per treatment group) was sufficient to provide 90% power to demonstrate therapeutic non-inferiority of the NanoTab System versus the IV PCA MS treatment in success rate. This calculation was based on a one-sided test with α=0.025 and a non-inferiority margin of -15%. To allow up to a 10% non-evaluable rate, approximately 390 patients were enrolled in this study.

Randomisation

A stratified randomization was applied in this study with age (< 65 years and > 65 years) and the type of surgery (knee and other surgeries) as stratification factors. Patients who met the eligibility requirements were randomized equally to receive either the NanoTab System or IV PCA MS within each of four stratification combination groups across all study sites.

Blinding (masking)

This was on open-label study.

Statistical methods

Statistical Study Conduct:

A planned interim data analysis was performed for this study based on study data collected from 173 patients who had primary efficacy data. The proportion of patients who rated their method of pain control “good” or “excellent” was calculated based on this interim data set. There was no adjustment of the original sample size for this study based on the results obtained from this interim data analysis.

Analysis Populations

The main analysis of the primary and secondary efficacy endpoints was performed on the intent-to-treat (ITT) population, which included all randomized patients who received study drug.

Completers were patients who completed a minimum of 48 hours in the study. The primary efficacy endpoint, success rate at 48 hours based on the PGA data, and secondary efficacy endpoint, success rate at 48 hours based on the HPGA data were analyzed for the completers.

All randomized patients who received at least one dose of study drug were included in the safety analysis and summaries.

Statistical Analysis of the Primary Efficacy Variable

The primary efficacy analysis was the construction of the 95% confidence interval of the difference in success rate between two treatment groups (Sufentanil NanoTab PCA System minus morphine IV PCA). This success rate was the proportion of patients who rated “good” or “excellent” on the Patient Global Assessment of method of pain control over the 48-hour study period using the four-point scale where 1=poor, 2=fair, 3=good and 4=excellent. If the lower boundary of this confidence interval of the difference in success rate was not less than -15%, the Sufentanil NanoTab PCA System/15 mcg treatment would be considered non-inferior to the morphine IV PCA treatment. In addition, a two-sample one-sided Z test on proportions of the primary efficacy endpoint against the lower equivalence margin (-15%) was performed at the $\alpha = 0.025$ significance level. A two-sided superiority test was also performed on this primary efficacy variable.

Continuous Secondary Efficacy Variables

An ANOVA model or ANCOVA model was used for the analysis of continuous secondary efficacy endpoints. The ANOVA model included treatment, centre, and surgery type (knee, hip, and abdominal) factors. The parallel lines ANCOVA model included treatment, centre, and surgery type factors, and baseline pain intensity as a covariate. The unequal slope ANCOVA model included treatment, centre, and surgery type factors, and baseline pain intensity covariate by treatment interaction factor. The final ANCOVA model was selected from a series of ANCOVA models, using the measurement as the dependent variable. The model selection process was based on the procedure presented by Milliken and Johnson (2001). Tests of effects were based on the Type III analysis in SAS PROC GLM.

The least squares (LS) mean of each treatment and its 95% CI were presented. A 95% CI of the difference between the NanoTab System treatment and IV PCA MS treatment (NanoTab System minus IV PCA MS) in the mean of these continuous secondary efficacy measurements was constructed.

Categorical Secondary Efficacy Variables

For the analysis of ordinal categorical data, a Cochran-Mantel-Haenszel test of general association stratified by age group and surgery type with modified ridit scores was used for the comparison between two treatment groups For the analysis of the dichotomous outcome data, a two-sample Z test on two proportions between the NanoTab System and IV PCA MS was performed.

Time to Event Data

The survival analysis method was used to analyse the time to event data. Kaplan-Meier product limit estimators of cumulative rates of patients reaching the event (i.e., termination due to inadequate analgesia) at follow-up time points was calculated. A log-rank test was used to compare the two treatment groups.

Baseline Comparability

Demographics and baseline characteristics were summarized by treatment group for all randomized patients. Data were pooled for all study centres for baseline data analysis. A two sample t-test was used to analyse the numeric variables. The equality of variances was examined using an F-test before applying the two-sample t-test. The Fisher's Exact test was used to analyse the categorical data. Similar summaries were performed separately for the ITT population, Completers, and the safety population.

Missing Data

For patients who terminated prematurely prior to the 48-hour study period due to reasons other than adverse event or lack of efficacy, the last observed response on the PGA was used for the derivation of the primary efficacy endpoint. For patients who terminated prematurely prior to the 48-hour study period due to adverse event or lack of efficacy, they were considered as a failure for the derivation of the primary efficacy endpoint. For ITT patients who did not provide any PGA data, they were considered as a failure for the derivation of the primary efficacy endpoint.

For patients missing pain intensity, PR, or RASS data, the following methods were applied to impute the missing data at evaluation time points for the duration of study period:

(1) Missing data were first imputed on a patient-by-patient basis by last observation carried forward (LOCF) method between two observed pain scale values.

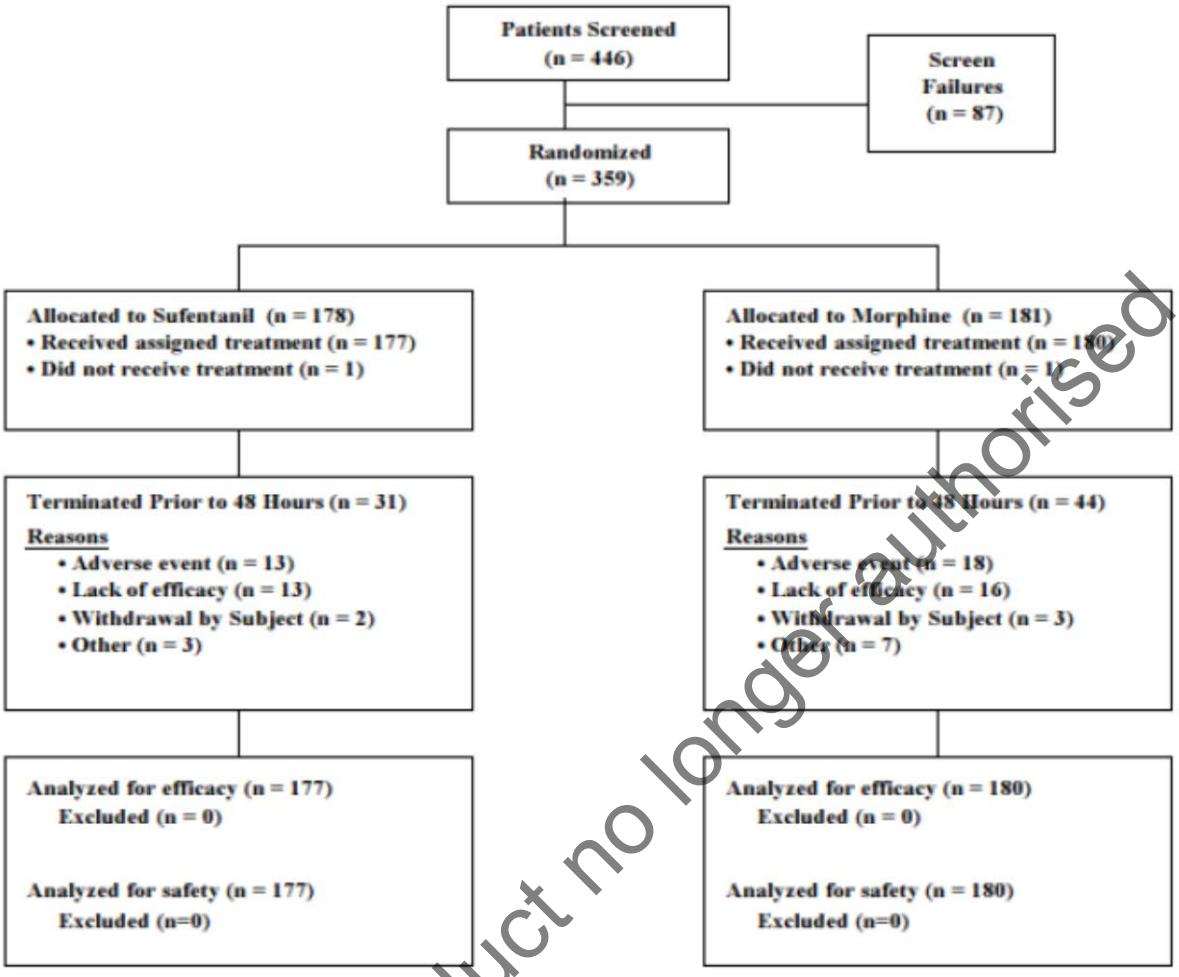
(2) Data occurring after a patient terminated from study or did not provide any follow-up data after last available data prior to the end the study period, the pain scale values at follow-up time points were imputed on a patient-by-patient basis described below.

The LOCF method was used to impute any remaining missing data points after termination due to reasons other than AEs up to the end of the study period. For patients who prematurely terminated from the study due to an AE, a worst observation carried forward (WOCF) method was used to impute the remaining missing data points up to the end of the study. The worst observation was the smaller number between zero and the last PID prior to termination. For patients who used any supplemental opioid medication during the study period, the worst observed pain intensity and PR score prior to the use of supplemental opioid medication were carried throughout a follow-up 1-hour time interval.

Results

Participant flow

Figure 1: CONSORT Flow Diagram



A total of 359 patients were randomized in this study; 2 patients did not receive study drug (one in each treatment group) leaving 357 patients who were randomized, received study drug and were included in the ITT and safety populations. Of these 357 patients, 282 (79.0%) completed the 48-hour study period (Completers) and were included in the analysis of the primary efficacy endpoint for Completers.

A total of 97 Completers elected to continue in the study beyond 48 hours and 67 continued through 72 hours, of whom 40 were in the sufentanil group and 27 in the morphine group.

Recruitment

Study Period:

Date first patient enrolled: 11 April 2012

Date last patient completed: 02 November 2012

Conduct of the study

There were three minor amendments to Protocol IAP309. They were not considered to have an impact on the conduct of the trial.

There was a small number of protocol deviations; i.e. some patients were randomized but not dosed. These patients were then excluded from the efficacy and safety analyses.

Baseline data

Provides an overview of the demographics of the study population.

Table 13 Demographics and baseline characteristics

IAP309	NanoTab System (n=177)	IV PCA MS (n=180)	Total (n=357)
Age (years)			
< 65	85 (48.0%)	85 (47.2%)	170 (47.6%)
≥ 65	92 (52.0%)	95 (52.8%)	187 (52.4%)
Mean (SD)	63.8 (12.1)	64.0 (12.6)	63.9 (12.4)
Min, max	19.0, 87.0	20.0, 88.0	19.0, 88.0
Sex			
Male	54 (30.5%)	72 (40.0%)	126 (35.3%)
Female	123 (69.5%)	108 (60.0%)	231 (64.7%)
Race			
White	160 (90.4%)	162 (90.0%)	322 (90.2%)
Black or African American	17 (9.6%)	17 (9.4%)	34 (9.5%)
Other	0	1 (0.6%)	1 (0.3%)
Ethnicity			
Hispanic or Latino	1 (0.6%)	1 (0.6%)	2 (0.6%)
Not Hispanic or Latino	176 (99.4%)	178 (99.4%)	354 (99.4%)
Caucasian	159 (89.8%)	161 (89.4%)	320 (89.6%)
Not Caucasian	18 (10.2%)	19 (10.6%)	37 (10.4%)
Weight (kg)			
Mean (SD)	84.3 (22.0)	87.1 (22.3)	85.7 (22.2)
Min, max	43.0, 152.0	40.4, 192.0	40.4, 192.0
Body Mass Index (kg/m^2)			
< 30	105 (59.3%)	99 (55.0%)	204 (57.1%)
≥ 30	72 (40.7%)	81 (45.0%)	153 (42.9%)
Mean (SD)	29.5 (6.3)	30.3 (6.6)	29.9 (6.4)
Min, max	18.3, 48.3	15.8, 53.7	15.8, 53.7
Type of Surgery			
Knee	56 (31.6%)	60 (33.3%)	116 (32.5%)
Hip	84 (47.5%)	78 (43.3%)	162 (45.4%)
Abdominal	37 (20.9%)	42 (23.3%)	79 (22.1%)

Source: Table 14.1.6.

SD: standard deviation; ITT: intent-to-treat; IV: intravenous; MS: morphine sulfate; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia.

Numbers analysed

The main analysis of the efficacy data used the ITT population, which included all randomized patients who received study drug. Additional analyses of the primary efficacy variable (PGA of method of pain

control at 48 hours) and select secondary efficacy variables (time-weighted SPID, TOTPAR, and time-weighted SPRID) were performed for Completers, i.e., all patients who received treatment and completed a minimum of 48 hours in the study.

Outcomes and estimation

Primary endpoint (PGA of Method of Pain Control at 48 Hours (PGA48))

A higher proportion of patients in the NanoTab System group (78.5%) responded good or excellent on the PGA48 than in the IV PCA MS group (65.6%). This difference was statistically significant for both non-inferiority ($p < 0.001$) and for treatment effect ($p = 0.007$). The criteria for non-inferiority was based on a lower margin of -15% for the 95% CI of the difference of PGA48 success rates between the two treatment groups.

The proportion of patients who responded excellent on the PGA48 was also higher in the NanoTab System group (42.9%) than in the IV PCA MS group (30.6%), and this difference was statistically significant for both non-inferiority ($p < 0.001$) and for treatment effect ($p = 0.016$).

Table 14 Proportion of patients reporting success on PGA48:ITT population

Success on PGA48	NanoTab System (n=177)	IV PCA MS (n=180)	Non-Inferiority P-value [1]	Treatment P-value [2]
Yes 95% CI	139 (78.5%) (72.48%, 84.58%)	118 (65.6%) (58.61%, 72.50%)	< 0.001	0.007
NanoTab System minus IV PCA MS 95% CI	12.90% (3.69%, 22.11%)	NA		

Source: Table 14.2.1.

CI: confidence interval; ITT: intent-to-treat; IV: intravenous; MS: morphine sulfate; NA: not applicable; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia; PGA48: patient global assessment of method of pain control at 48 hours; Success: "good" or "excellent" rating on PGA48.

[1] The p-value for the test of non-inferiority of NanoTab System against IV PCA MS based on the two-sample one-sided Z test for two proportions against delta = -0.15.

[2] The p-value for the comparison between two treatment groups was based on the Z test for the difference in proportions between the two groups.

Secondary efficacy endpoints

PGA24 and PGA72 and Proportion of Patients who Responded in Each Category

Table 15 Proportion of patients who responded in each category of the PGA

	NanoTab System (n=177)	IV PCA MS (n=180)	P-value [1]
24 Hours; n	163	160	
Poor	5 (3.1%)	8 (5.0%)	0.075
Fair	21 (12.9%)	33 (20.6%)	
Good	77 (47.2%)	78 (48.8%)	
Excellent	60 (36.8%)	41 (25.6%)	
48 Hours; n	149	138	
Poor	1 (0.7%)	1 (0.7%)	0.056
Fair	11 (7.4%)	25 (18.1%)	
Good	62 (41.6%)	58 (42.0%)	
Excellent	75 (50.3%)	54 (39.1%)	
72 Hours; n	42	30	
Poor	0 (0.0%)	0 (0.0%)	0.044
Fair	0 (0.0%)	3 (10.0%)	
Good	11 (26.2%)	11 (36.7%)	
Excellent	31 (73.8%)	16 (53.3%)	

Source: Table 14.2.5.

IV: intravenous; MS: morphine sulfate; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia

[1] The p-value for the comparison between two treatment groups was based on Cochran-Mantel-Haenszel test of general association stratified by age group and surgery type with modified ridit scores.

A higher proportion of patients in the NanoTab System group responded good or excellent on the PGA24 and PGA72 compared with the IV PCA MS group . These differences were statistically significant at both time points for non-inferiority ($p < 0.001$) and for treatment effect ($p < 0.05$).

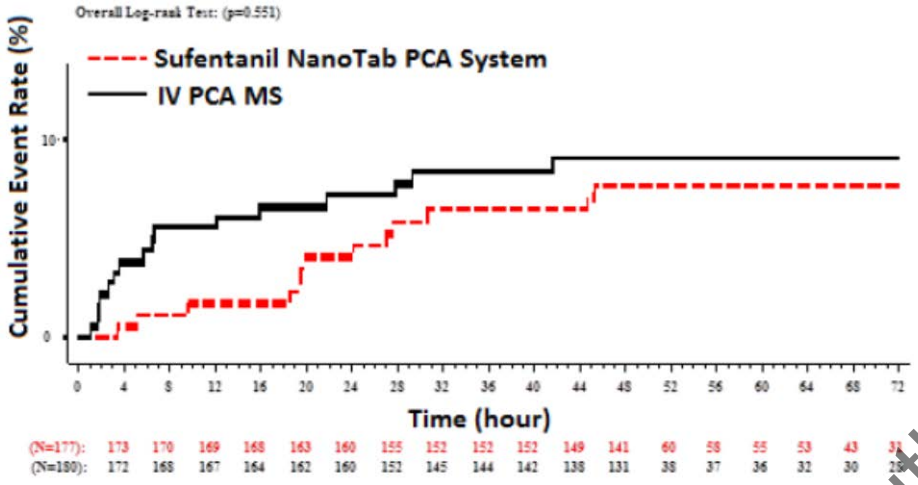
Numerically more patients responded excellent and fewer patients responded fair on the PGA24, PGA48, and PGA72 in the NanoTab System group than in the IV PCA MS group. However, for the ITT population, the difference between treatment groups for the proportion of patients responding in each category of the PGA was only statistically significant for the PGA72 ($p = 0.044$). Study Completers were defined as those patients who completed 48 hours of study treatments and assessments. Completers were able to continue in the study until 72 hours. For Completers, the difference between treatment groups for the proportion of patients responding in each category of the PGA was statistically significant at all times (PGA24: $p = 0.021$; PGA48: $p = 0.030$; PGA72: $p = 0.044$).

HPGA of Method of Pain Control

There were statistically significant differences between treatment groups for the proportion of HCPs who responded in each category of the HPGA24, HPGA48, and HPGA72 ($p = 0.002$, $p = 0.044$, and $p = 0.008$, respectively for the ITT population), with more responses of excellent for the NanoTab System group than for the IV PCA MS group at all time points. Similar results were observed for Study Completers ($p < 0.001$, $p = 0.025$, $p = 0.008$ for HPGA24, HPGA48, and HPGA72, respectively).

Terminations due to Inadequate Analgesia

Figure 4: Kaplan Meier Cumulative Event Rates for Time to Termination from the Study Due to Inadequate Analgesia: ITT Population



Source: Figure 14.2.6.

Sufentanil = Sufentanil NanoTab PCA System/15 mcg; Morphine = IV PCA MS.

P-value based on the log-rank test between treatment groups.

Thirteen patients (7.3%) in the NanoTab System group and 16 patients (8.9%) in the IV PCA MS group discontinued due to inadequate analgesia prior to 48 hours. There were no statistically significant differences between treatment groups for the proportion of patients who discontinued due to inadequate analgesia or for the time to discontinuation due to inadequate analgesia.

Patient and Nurse Ease of Care Questionnaires

Higher (superior) mean scores were observed for patients in the NanoTab System group compared with the IV PCA MS group for the patient EOC Total Score (combined analysis of questions 1-21; $p < 0.001$) and all subscale analyses ($p < 0.05$ for all) on the patient EOC questionnaire. Patients in the NanoTab System group had an overall Satisfaction Score (combined analysis of questions 22 and 23) higher than in the IV PCA MS group ($p = 0.004$).

For the nurse EOC questionnaire, there were statistically higher (superior) mean scores for the NanoTab System compared to IV PCA MS for nurse EOC Total Score (combined analysis of questions 1-20) and overall Satisfaction Score (combined analysis of questions 21 and 22) ($p = 0.017$ and $p < 0.001$, respectively). Subscale analysis demonstrated significantly lower “bothersome” scores for the NanoTab System compared to IV PCA MS ($p = 0.006$).

Time-Weighted Summed Pain Intensity Difference (SPID), Total Pain Relief (TOTPAR), and Summed Pain Relief Intensity Difference (SPRID)

Table 16 Analysis of Time-Weighted Summed Pain Intensity Difference at 24, 48 and 72 hours: ITT population

	NanoTab System (n=177)	IV PCA MS (n=177)	Difference†	P-value [1]
Baseline Pain Intensity				
LS mean (SEM)	5.55 (0.12)	5.85 (0.11)	NA	0.028
95% CI	(5.32, 5.78)	(5.63, 6.07)		
SPID24				
LS mean (SEM)	34.38 (3.88)	30.72 (3.75)	3.66 (4.55)	0.422
95% CI	(26.74, 42.01)	(23.35, 38.09)	(-5.30, 12.61)	
SPID48				
LS mean (SEM)	77.94 (8.40)	72.33 (8.10)	5.61 (9.84)	0.569
95% CI	(61.43, 94.46)	(56.40, 88.27)	(-13.76, 24.97)	
SPID72				
LS mean (SEM)	133.62 (13.45)	122.51 (12.98)	11.11 (15.77)	0.482
95% CI	(107.17, 160.07)	(96.99, 148.04)	(-19.91, 42.13)	

Source: Tables 14.2.19, 14.2.20, and 14.2.21.

†NanoTab System minus IV PCA MS.

CI: confidence interval; ITT: intent-to-treat; IV: intravenous; LS: least squares; MS: morphine sulfate; NA: not applicable; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia; SEM: standard error of the LS mean.

For the baseline pain intensity, the LS mean and SEM are estimated from the ANOVA model that includes treatment,center, and surgery type (knee, hip, and abdominal) factors.

For the time-weighted SPID, the LS mean and SEM were estimated from the ANCOVA model that includes treatment, center, and surgery type factors, and baseline pain intensity as a covariate.

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

Mean baseline pain intensity scores were significantly higher in the IV PCA MS group than in the NanoTab System group (5.85 vs. 5.55; p = 0.028), however this difference is not clinically meaningful and any impact is lessened by a pain intensity difference (PID), SPID or SPRID analysis.

There were no statistically significant differences between treatment groups for mean time-weighted SPID24, SPID48, or SPID72, although significantly higher SPID scores were observed in the NanoTab System group compared with the IV PCA MS group at 2, 4, 6, 8, and 10 hours (p < 0.05). There were no statisitcally significant differences between treatment groups for the time-weighted SPID48 scores for any subgroups of patients based on age, sex, race, or BMI.

Mean TOTPAR48 scores were numerically higher (p = 0.058) in the NanoTab System group compared to the IV PCA MS group. TOTPAR24 and TOTPAR72 scores were significantly higher in the NanoTab System group than in the IV PCA MS group (p < 0.05). Higher TOTPAR scores were also observed in the NanoTab System group compared with the IV PCA MS group from 2 to 24 and from 52 to 72 hours.

There were no statistically significant differences between treatment groups for mean time-weighted SPRID24, SPRID48, or SPRID72, although significantly higher (i.e., better) SPRID scores were observed in the NanoTab System group compared with the IV PCA MS group at 2, 4, 6, 8, 10, and 12 hours (p < 0.05).

Pain Intensity and Pain Intensity Difference by Evaluation Timepoint

Significantly lower pain intensity scores and significantly higher (better) PID scores were observed in the NanoTab System group compared with the IV PCA MS group at 1, 2, and 4 hours (p < 0.01). There were no statistically significant differences between NanoTab System group and IV PCA MS group for pain intensity at any of the remaining evaluation time points.

Pain Relief by Evaluation Time point

Significantly higher PR scores were observed in the NanoTab System group compared with the IV PCA MS group at 1, 2, and 4 hours and from 48 to 72 hours ($p < 0.05$). There were no statistically significant differences between NanoTab System group and IV PCA MS group for PR scores at any of the remaining evaluation time points.

Pain Relief Intensity Difference by Evaluation Time point

Significantly higher PRID scores were observed in the NanoTab System group compared with the IV PCA MS group at 1, 2, 4, and 6 hours ($p < 0.05$). There were no statistically significant differences between NanoTab System group and IV PCA MS group for PRID scores at any of the remaining evaluation time points.

Richmond Agitation and Sedation Scale (RASS)

Baseline RASS scores were similar in the two treatment groups. There were no statistically significant differences between treatment groups for time-weighted summed RASS24, RASS48, or RASS72 scores or for time-weighted summed RASS scores or RASS scores at any evaluation time point.

Study Drug Dosing, Inter-Dosing Interval, and Supplemental Morphine Use

Patients in the NanoTab System group had a significantly longer inter-dosing interval compared with patients in the IV PCA MS group (81.1 vs. 46.2 minutes, respectively; $p < 0.001$). and also used significantly fewer doses of study drug during the 48-hour study period compared with the IV PCA MS group (44.4 vs. 69.5, respectively; $p < 0.001$). The mean number of supplemental morphine doses (2 mg slow bolus) used by patients in the NanoTab System group was significantly higher than in the IV PCA MS group (1.3 vs. 0.5; $p < 0.001$), although not clinically meaningful.

System-Related Events

In the NanoTab System group, 15 (8.5%) patients had a system error screen (“system nonfunctional”) and 2 (1.1%) of patients required re-education on the use of the device. System errors with the NanoTab System were in accordance with the system design and known use errors and resulted in a short interruption of analgesia while the system was replaced. No system errors were associated with a potential safety concern. In the IV PCA MS group, 9 (5.0%) patients, had an IV line issue, 3 (1.7%) had IV pump malfunction, 1 (0.6%) required re-education, and 1 (0.6%) had a programming error.

Ancillary analyses

The results of the primary endpoint analysis by demographic variables, BMI and by type of surgery are presented in Table 17 below.

Table 17 Proportion of patients reporting success on the PGA48 by demographic variables and BMI

Responded Good or Excellent	NanoTab System	IV PCA MS	Difference†	P-value [1]	P-value [2]
Age < 65 Yrs: n	85	85			
Yes	69 (81.2%)	56 (65.9%)	15.30%	< 0.001	0.024
95% CI	(72.87%, 89.49%)	(55.80%, 75.96%)	(2.24%, 28.36%)		
Age ≥ 65 Yrs: n	92	95			
Yes	70 (76.1%)	62 (65.3%)	10.80%	< 0.001	0.105
95% CI	(67.37%, 84.80%)	(55.69%, 74.84%)	(-2.15%, 23.75%)		
Male Patients: n	54	72			
Yes	41 (75.9%)	47 (65.3%)	10.60%	< 0.001	0.199
95% CI	(64.52%, 87.33%)	(54.28%, 76.27%)	(-5.24%, 26.44%)		
Female Patients: n	123	108			
Yes	98 (79.7%)	71 (65.7%)	14.00%	< 0.001	0.017
95% CI	(72.56%, 86.79%)	(56.79%, 74.69%)	(2.57%, 25.43%)		
Caucasian Patients: n	159	161			
Yes	124 (78.0%)	106 (65.8%)	12.20%	< 0.001	0.015
95% CI	(71.55%, 84.43%)	(58.51%, 73.16%)	(2.45%, 21.95%)		
Non-Caucasian Patients: n	18	19			
Yes	15 (83.3%)	12 (63.2%)	20.10%	0.008	0.169
95% CI	(66.12%, 100%)	(41.47%, 84.85%)	(-7.60%, 47.80%)		
BMI < 30 kg/m^2: n	105	99			
Yes	82 (78.1%)	62 (62.6%)	15.50%	< 0.001	0.015
5% CI	(70.18%, 86.01%)	(53.10%, 72.16%)	(3.11%, 27.89%)		
BMI ≥ 30 kg/m^2: n	72	81			
Yes	57 (79.2%)	56 (69.1%)	10.10%	< 0.001	0.156
95% CI	69.79%, 88.55%)	(59.08%, 79.20%)	(-3.65%, 23.85%)		

Source: Tables 14.2.59, 14.2.60, 14.2.61, 14.2.62, 14.2.63, 14.2.64, 14.2.70, and 14.2.71.

†NanoTab System minus IV PCA MS.

BMI: body mass index; CI: confidence interval; ITT: intent-to-treat; IV: intravenous; MS: morphine sulfate; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia; PGA48: patient global assessment of method of pain control at 48 hours; Success: "good" or "excellent" rating on PGA48.

[1] The p-value for the test of non-inferiority of NanoTab System against IV PCA MS was based on the two-sample one-sided Z test for two proportions against delta = -0.15.

[2] The p-value for the comparison between two treatment groups was based on the Z test for the difference in proportions between two groups.

Responded Good or Excellent	NanoTab System	IV PCA MS	Difference†	P-value [1]	P-value [2]
Knee Surgery: n	56	60			
Yes	39 (69.6%)	38 (63.3%)	6.30%	0.008	0.473
95% CI	(57.60%, 81.69%)	(51.14%, 75.53%)	(-10.84%, 23.44%)		
Non-Knee Surgery: n	121	120			
Yes	100 (82.6%)	80 (66.7%)	15.90%	< 0.001	0.005
95% CI	(75.90%, 89.39%)	(58.23%, 75.10%)	(5.10%, 26.70%)		
Orthopedic Surgery: n	140	138			
Yes	109 (77.9%)	90 (65.2%)	12.70%	< 0.001	0.019
95% CI	(70.98%, 84.74%)	(57.27%, 73.16%)	(2.19%, 23.21%)		
Hip Surgery: n	84	78			
Yes	70 (83.3%)	52 (66.7%)	16.60%	< 0.001	0.014
95% CI	(75.36%, 91.30%)	(56.20%, 77.13%)	(3.45%, 29.75%)		
Abdominal Surgery: n	37	42			
Yes	30 (81.1%)	28 (66.7%)	14.40%	0.002	0.148
95% CI	(68.46%, 93.70%)	(52.41%, 80.92%)	(-4.63%, 33.43%)		

Source: Tables 14.2.65, 14.2.66, 14.2.67, 14.2.68, and 14.2.69.
CI: confidence interval; ITT: intent-to-treat; IV: intravenous; MS: morphine sulfate; NanoTab System: Sufentanil NanoTab PCA System/15 mcg; PCA: patient-controlled analgesia; PGA48: patient global assessment of method of pain control at 48 hours; Success: "good" or "excellent" rating on PGA48.

†NanoTab System minus IV PCA MS.

[1] The p-value for the test of non-inferiority of NanoTab System against IV PCA MS was based on the two-sample one-sided Z test for two proportions against delta = -0.15.

[2] The p-value for the comparison between two treatment groups was based on the Z test for the difference in proportions between two groups.

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 18. Summary of efficacy for trial IAP310

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® PCA System/15 mcg for the Treatment of Post- Operative Pain in Patients after Open Abdominal Surgery		
Study identifier	**IAP310**	
Design	Multicenter, Randomized, Double-Blind, Placebo-Controlled pivotal trial	
	Duration of main phase: Duration of Run-in phase:	72 hours Not applicable
Hypothesis	Superiority of the Sufentanil NanoTab PCA System/15 µg over the Placebo NanoTab PCA System for the management of acute post-operative pain after open abdominal surgery	
Treatments groups	Test	Sufentanil NanoTab 15 microgram, number randomized: 119

	Reference		Placebo NanoTab, number randomized: 59
Endpoints and definitions	Primary endpoint	SPID48	Time-weighted summed pain intensity difference (SPID) over the 48-hour study period.
	Secondary endpoints	Modified SPID48	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 48-hour study period
		SPID24	Time-weighted summed pain intensity difference over 24-hour study period
		Modified SPID24	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 48-hour study period
		SPID72	Time-weighted summed pain intensity difference over 72-hour study period
		Modified SPID72	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 72-hour study period
		TOTPAR24	Time-weighted total pain relief (TOTPAR) over the 24-hour study period
		TOTPAR48	Time-weighted total pain relief (TOTPAR) over the 48-hour study period
		TOTPAR72	Time-weighted total pain relief (TOTPAR) over the 72-hour study period
			Proportion of patients requiring rescue medication due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
			Total amount of supplemental and rescue morphine utilized over the 48-hour study period
			Proportion of patients and healthcare professionals who responded to the global assessments as “excellent” or “good”
		PI	Pain intensity (PI) at each evaluation time point
		PR	Pain relief (PR) at each evaluation time point
		PRID	Pain relief intensity difference (PRID) at each evaluation time point. The PRID is the sum of PR and PID
			Total number of study drug doses used over 24, 48, and 72-hour study period and average hourly use
		TOTPAR24	Modified time-weighted total pain relief over the 24-hour study period without including any PR data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint

		TOTPAR48	Modified time-weighted total pain relief over the 48-hour study period without including any PR data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint
		TOTPAR72	Modified time-weighted total pain relief over the 72-hour study period without including any PR data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint
		SPRID24	Time-weighted summed pain relief intensity difference (SPRID) over 24-hour study period
		SPRID48	Time-weighted summed pain relief intensity difference over the 48-hour study period
		SPRID72	Time-weighted summed pain relief intensity difference over the 72-hour study period
			Proportion of patients who terminate from the study due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
Database lock	Study was initiated on 6 March 2012 and completed on 11 January 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, primary endpoint at 48 hours		
Descriptive statistics and estimate variability	Treatment group	Sufentanil sublingual tablet	Placebo
	Number of subject	115	57
	primary endpoint SPID48 (LS mean)	105.6	55.58
	SEM	10.14	13.11
	SPID24 (LS mean)	48.44	18.62
	SEM	4.71	6.1
	SPID72	171.05	100.75
	SEM	16.17	20.91
	TOTPAR24	44.82	30.26
	SEM	2.29	2.96
	TOTPAR48	93.32	68.38
	SEM	5.14	6.65

	TOTPAR72	146.17	108.93
	SEM	8.46	10.95
	Proportion of subjects who discontinued over the 48-hour trial period	17.4 %	31.6 %
	Proportion of subjects requiring rescue opioid over the 48-hour trial period	33.0 %	66.7 %
	Cumulative rescue /supplemental opioid use opioid doses consumed over 48 hours (Mean number of doses)	1.8	3.8
	total number of study medication during the first 12 h, mean (SD)	11 (6) difference versus placebo:p=0.054	13 (7.2)
	total number of study medication during the first 24 h, mean (SD)	20 (11.9) difference vs. placebo: p=0.46	21 (13)

Effect estimate per comparison	Primary endpoint SPID48	Comparison groups		
			Sufentanil	Placebo
		LS mean (SEM)	105.6 (10.14)	55.58 (13.11)
		95 % CI of the LS mean	(85.88, 125.62)	(29.69, 81.48)
		LS mean difference (SEM)	50.02 (15.25)	
		95 % CI of the LS mean difference	(19.89, 80.14)	
		p-value	0.001	
	Time-weighted SPID24		Sufentanil	Placebo
		LS mean (SEM)	48.44 (4.71)	18.62 (6.10)
		LS mean difference (SEM)	29.82 (7.09)	
		95 % CI on the LS mean difference	(15.81, 43.83)	
		p-value	<0.001	
	Time-weighted SPID72		Sufentanil	Placebo
		LS mean (SEM)	171.05 (16.17)	100.75 (20.91)
		LS mean difference (SEM)	70.30 (24.33)	
		95 % CI on the LS mean difference	(22.24, 118.36)	
		p-value	0.004	
	TOTPAR24		Sufentanil	Placebo
		LS mean (SEM)	44.82 (2.29)	30.26 (2.96)
		LS mean difference (SEM)	14.56 (3.45)	
		95 % CI on the LS mean difference	(7.75, 21.36)	

		p-value		<0.001
	TOTPAR48		Sufentanil	Placebo
		LS mean (SEM)	93.32 (5.14)	68.38 (6.65)
		LS mean difference (SEM)	24.95 (7.74)	
		95 % CI on the LS mean difference	(9.66, 40.23)	
		p-value	0.002	
	TOTPAR72		Sufentanil	Placebo
		LS mean (SEM)	146.17 (8.46)	108.93 (10.95)
		LS mean difference (SEM)	37.24 (12.73)	
		95 % CI on the LS mean difference	(12.08, 62.39)	
		p-value	0.004	
Notes	statistically significant improvements in pain intensity and pain relief by 45 minutes after the start of study drug dosing			

Table 19. Summary of efficacy for trial IAP311

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® PCA System/15 mcg for the Treatment of Post- Operative Pain in Patients after Knee or Hip Replacement Surgery			
Study identifier	**IAP311**		
Design	Multicenter, Randomized, Double-Blind, Placebo-Controlled Pivotal Trial		
	Duration of main phase: Duration of Run-in phase:		72 hours not applicable
Hypothesis	Superiority of the Sufentanil NanoTab PCA System/15 mcg over Placebo NanoTab PCA System for the management of acute post-operative pain after total unilateral knee or total unilateral hip replacement surgery.		
Treatments groups	Test		Sufentanil NanoTab 15 microgram, number randomized: 321
	Reference		Placebo NanoTab, number randomized: 105
Endpoints and definitions	Primary endpoint	SPID48	Time-weighted summed pain intensity difference (SPID) over the 48-hour study period.
	Secondary endpoints	Modified SPID48	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 48-hour study period
		SPID24	Time-weighted summed pain intensity difference over 24-hour study period
		Modified SPID24	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 48-hour study period

		SPID72	Time-weighted summed pain intensity difference over 72-hour study period
		Modified SPID72	Modified time-weighted summed pain intensity difference without including any PI data collected after a patient received the first dose of rescue opioid in the calculation of this efficacy endpoint over the 72-hour study period
		TOTPAR24	Time-weighted total pain relief (TOTPAR) over the 24-hour study period
		TOTPAR48	Time-weighted total pain relief (TOTPAR) over the 48-hour study period
		TOTPAR72	Time-weighted total pain relief (TOTPAR) over the 72-hour study period
			Proportion of patients requiring rescue medication due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
Endpoints and definitions	Secondary endpoints		Total amount of supplemental and rescue morphine utilized over the 48-hour study period
			Proportion of patients and healthcare professionals who responded to the global assessments as "excellent" or "good"
		PI	Pain intensity (PI) at each evaluation time point
		PR	Pain relief (PR) at each evaluation time point
		PRID	Pain relief intensity difference (PRID) at each evaluation time point. The PRID is the sum of PR and PID
			Total number of study drug doses used over 24, 48, and 72-hour study period and average hourly use
			Modified time-weighted TOTPAR over the 24-hour study period
			Modified time-weighted TOTPAR over the 48-hour study period
			Modified time-weighted TOTPAR over the 72-hour study period
		SPID24	Summed pain intensity difference over 24-hour study period
		SPID48	Summed pain intensity difference over 48-hour study period
		TOTPAR24	Total pain relief over the 24-hour study period
		TOTPAR48	Total pain relief over the 48-hour study period
		TOTPAR72	Total pain relief over the 72-hour study period
Database lock	First patient was enrolled on 22 August 2012 and the last patient completed the study on 07 April 2013		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, primary endpoint at 48 hours post surgical		
Descriptive statistics and estimate variability	Treatment group	Sufentanil sublingual tablet	Placebo
	Number of subject	315	104
	SPID48 (LS mean)	76.24	-11.35
	SEM	7.02	10.55
	SPID24 (LS mean)	32.02	-8.98
	SEM	3.25	4.89
	SPID72 (LS mean)	134.58	-2.84
	SEM	11.44	17.18
	Time-weighted TOTPAR24 (LS mean)	42.77	25.80
	SEM	1.37	2.06
	TOTPAR48 (LS mean)	91.29	53.45
	SEM	3.00	4.50
	TOTPAR72	145.67	84.52
	SEM	5.03	7.55
	Proportion of subjects who discontinued over the 48-hour trial period	14.3 %	48.1 %
	Proportion of subjects requiring rescue opioid over the 48-hour trial period	50.8 %	73.1 %
	Cumulative rescue /supplemental opioid use opioid doses consumed over 48 hours (Mean number of doses)	2.2	3.8
	total number of study medication during the first 12 h, mean (SD)	12 (6.6) difference versus placebo:p=0.199	13 (7.7)
	total number of study medication during the first 24 h, mean (SD)	22 (11.9) difference vs. placebo: p=0.626	21 (13.9)
Effect estimate	Primary endpoint	Comparison groups	

per comparison	SPID48		Sufentanil	Placebo
		LS mean (SEM)	76.24 (7.02)	-11.35 (10.55)
		95 % CI on the LS mean	(62.43, 90.05)	-32.08, 9.38
		LS mean difference (SEM)	87.59 (10.88)	
		95 % CI on the LS mean difference	66.20, 108.98	
		p-value	<0.001	
	Time-weighted SPID24		Sufentanil	Placebo
		LS mean (SEM)	32.02 (3.25)	-8.98 (4.89)
		LS mean difference (SEM)	41.01	
		95 % CI on the LS mean difference	(31.09, 50.92)	
		p-value	<0.001	
	Time-weighted SPID72		Sufentanil	Placebo
		LS mean (SEM)	134.58 (11.44)	-2.84 (17.18)
		LS mean difference (SEM)	137.42 (17.73)	
		95 % CI on the LS mean difference	(102.57, 172.27)	
		p-value	<0.001	
	Time-weighted TOTPAR24		Sufentanil	Placebo
		LS mean (SEM)	42.77 (1.37)	25.80 (2.06)
		LS mean difference (SEM)	16.97 (2.13)	
		95 % CI on the LS mean difference	(12.79, 21.15)	
		p-value	<0.001	
	TOTPAR48		Sufentanil	Placebo
		LS mean (SEM)	91.29 (3.00)	53.45 (4.50)
		LS mean difference (SEM)	37.84 (4.65)	
		95 % CI on the LS mean difference	(28.70, 46.97)	
		p-value	<0.001	
	TOTPAR72		Sufentanil	Placebo
		LS mean (SEM)	145.67 (5.03)	84.52 (7.55)
		LS mean difference (SEM)	61.15 (7.79)	
		95 % CI on the LS mean difference	(45.83, 76.46)	
		p-value	<0.001	
Notes	statistically significant improvements in pain intensity and pain relief by 45 minutes after the start of study drug dosing			

Table 20. Summary of efficacy for trial IAP309

Title: A Multicentre, Randomized, Open-Label, Parallel-Group Trial to Compare the Efficacy and Safety of the Sufentanil NanoTab® PCA System/15 µg to Intravenous Patient-Controlled Analgesia with Morphine for the Treatment of Acute Post-Operative Pain

Study identifier	IAP309		
Design	This study was designed as an open-label, randomized, active comparator study to compare the efficacy and safety of the NanoTab System with IV PCA MS. Validated instruments were used to assess pain intensity, pain relief, and global assessments during the study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Date first patient enrolled: 11 April 2012 Date last patient completed: 02 November 2012 not applicable not applicable	
Hypothesis	The primary efficacy analysis was the construction of the 95% confidence interval of the difference in success rate between two treatment groups (Sufentanil NanoTab PCA System/15 µg treatment minus morphine IV PCA treatment). This success rate is the proportion of patients who rated "good" or "excellent" on the Patient Global Assessment of method of pain control over the 48-hour study period using the four-point scale where 1=poor, 2=fair, 3=good and 4=excellent. If the lower boundary of this confidence interval of the difference in success rate is not less than -15%, the Sufentanil NanoTab PCA System/15 mcg treatment would be considered non-inferior to the morphine IV PCA treatment. A two-sided superiority test was also performed on this primary efficacy variable. (Noninferiority)		
Treatments groups	**Sufentanil NanoTab PCA System**		Sufentanil 15 µg NanoTab PCA System for 48 hours postoperatively, 178 patients randomized
	IV PCA pump with Morphine Sulfate		IV PCA pump with MS, 1 mg/dose for 48 hours postoperatively, 181 patients randomized
Endpoints and definitions	Primary endpoint	**PGA48**	Success for the PGA48, defined as the **proportion of patients who responded "good" or "excellent"** to the question "Overall, how would you rate the method of pain control?" Patient's response on the PGA of method of pain control over the 48-hour study period using the 4-point scale where 1=poor, 2=fair, 3=good and 4=excellent.
	Secondary endpoint	**Termin**	Proportion of patients who terminated from the study due to inadequate analgesia over the 48-hour study period
	Secondary endpoint	**SPID48**	Time-weighted summed pain intensity differences from baseline over the 48-hour study periods

	Secondary endpoint	**#Doses**	Number of doses used over the 48-hour study period
Database lock	<date>		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat at 48 hours		
Descriptive statistics and estimate variability	Treatment group	Sufentanil Nano Tab System	IV PCA - pump with Morphine Sulfate
	Number of subject	177	180
	PGA48 n (%)	**139** (78.5)	**118** (65.6)
	95% CI	72.48; 84.58	58.61; 72.50
	Termin n (%)	**13** (7.3)	**16** (8.9)
	95% CI of difference in proportion	3.50; 11.19	4.76; 13.05
	SPID48	**77.94**	**72.33**
	95% CI	61.43; 94.46	56.40; 88.27
	#Doses	**44.39**	**69.44**
	95% CI	38.57; 50.21	63.83; 75.05

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

For further analysis of the clinical relevance in IAP309, IAP310 and IAP311, a responder analysis was performed to determine what proportion of subjects had at least a 30% and at least a 50% reduction in pain intensity, based on duration-adjusted time-weighted SPID. The results for SPID48 are shown in Table 21

Table 21 Proportion of subjects who had at least 30% and 50% reduction in pain intensity

48 hour SPID	Sufentanil N = 177	Morphine N = 177
At Least 30% Reduction in Pain Intensity from Baseline – n(%)		
Yes	101 (57.1%)	97 (54.8%)
No	76 (42.9%)	80 (45.2%)
95% CI of P(Yes)	(49.77%, 64.35%)	(47.47%, 62.13%)
Sufentanil minus Morphine		
Difference in P(Yes)	2.30%	NA
95% CI of Difference in proportions	(-8.04%, 12.64%)	
At Least 50% Reduction in Pain Intensity from Baseline – n(%)		
Yes	53 (29.9%)	56 (31.6%)
No	124 (70.1%)	121 (68.4%)
95% CI of P(Yes)	(23.20%, 36.69%)	(24.79%, 38.49%)
Sufentanil minus Morphine		
Difference in P(Yes)	-1.70%	NA
95% CI of Difference in proportions	(-11.31%, 7.91%)	

Intent-to-treat population of trial LAP310

48 hour SPID	Sufentanil N = 115	Placebo N = 57
At Least 30% Reduction in Pain Intensity from Baseline – n(%)		
Yes	69 (60.0%)	21 (36.8%)
No	46 (40.0%)	36 (63.2%)
95% CI of P(Yes)	(51.05%, 68.95%)	(24.32%, 49.36%)
Sufentanil minus Placebo		
Difference in P(Yes)	23.20%	NA
95% CI of Difference in proportions	(7.81%, 38.59%)	
At Least 50% Reduction in Pain Intensity from Baseline – n(%)		
Yes	43 (37.4%)	10 (17.5%)
No	72 (62.6%)	47 (82.5%)
95% CI of P(Yes)	(28.55%, 46.23%)	(7.67%, 27.42%)
Sufentanil minus Placebo		
Difference in P(Yes)	19.90%	NA
95% CI of Difference in proportions	(6.65%, 33.15%)	

Intent-to-treat population of trial IAP311

48 Hour SPID	Sufentanil N = 315	Placebo N = 104
At Least 30% Reduction in Pain Intensity from Baseline – n(%)		
Yes	173 (54.9%)	26 (25.0%)
No	142 (45.1%)	78 (75.0%)
95% CI of P(Yes)	(49.43%, 60.42%)	(16.68%, 33.32%)
Sufentanil minus Placebo		
Difference in P(Yes)	29.90%	NA
95% CI of Difference in proportions	(19.93%, 39.87%)	
At Least 50% Reduction in Pain Intensity from Baseline – n(%)		
Yes	98 (31.1%)	10 (9.6%)
No	217 (68.9%)	94 (90.4%)
95% CI of P(Yes)	(26.00%, 36.22%)	(3.95%, 15.28%)
Sufentanil minus Placebo		
Difference in P(Yes)	21.50%	NA
95% CI of Difference in proportions	(13.87%, 29.13%)	

Sufentanil 15 µg and placebo were given using the Zalviso administration device; morphine was administered using IVPCA.

P(Yes) = Proportion of subjects who had at least 30% reduction/50% reduction in pain intensity from baseline; CI = Confidence Interval; NA = Not applicable; IV = intravenous; PCA = patient controlled analgesia; SPID = sum of pain intensity difference.

Source: ZLV-147\att3, ZLV-147\att4, ZLV-147\att5, ZLV-147\att6

In both placebo-controlled trials (IAP310 and IAP311), the number of subjects with 30% and 50% pain reduction was higher in the sufentanil group than in the placebo group. In addition, more than 50% of the subjects in the sufentanil group experienced a clinically relevant 30% pain reduction, compared to less than 37% in the placebo group.

In IAP309, comparing sufentanil and morphine, there was a similar proportion of clinically relevant 30% pain reduction in both treatment groups. This confirms that sufentanil provides a clinically relevant decrease in pain intensity, which is at least comparable to the standard of care.

Clinical studies in special populations

Table 22

	Age 65-74 (Older subjects number /total number)	Age ≥75 (Older subjects number /total number)
Controlled Trials IAP309, 310, 311	185/607 (30.4 %)	116/607 (19.1 %)

39.5 % of the patients in the three phase III trials was aged 65 or older. Thus, there is sufficient amount of efficacy data in older adults available and efficacy does not have to be extrapolated to this demographic group.

Supportive study

ARX-C-004

An Open-Label Functionality, Safety, and Efficacy Study of the NanoTab Delivery System / ARX-F01 15 µg in Patients Undergoing Elective Unilateral Knee Replacement

This was an open-label, multicentre trial in patients 45 to 80 years of age who were undergoing elective unilateral knee replacement. Inclusion and exclusion criteria were comparable to those of protocols IAP309, IAP310 and IAP311. The primary objective of this study was to evaluate the functionality of the Sufentanil NanoTab PCA System 15 µg for patient self-administration. The System used in this trial was an earlier version with limited design features.

The secondary objectives were to evaluate the safety, efficacy, and tolerability of the Sufentanil NanoTab PCA System 15 µg for treatment of moderate-to-severe postoperative pain using patient ratings of pain intensity and pain relief scores over the 12-hour study period, percentage of patients terminated from the study due to inadequate analgesia, patient global assessment of efficacy and tolerability, and patient observations of the Sufentanil NanoTab PCA System.

The functionality of the Sufentanil NanoTab PCA System was assessed by study staff through inspection of:

• The patient's mouth immediately after dosing to document placement of the NanoTab

• The System's electronic display for confirmation of successful dosing or any error messages that indicate a dosing problem

30 patients were enrolled, received the study drug and were included in the analysis. 26 patients completed the full 12 hours of study drug dosing.

The outcomes from this study support the functionality of the nanotab - device combination. All enrolled patients completed the study without any Sufentanil NanoTab PCA System 15 µg failures. Two patients terminated the study due to inadequate analgesia. Total dose and dose interval were comparable to the 15 µg arms of the two phase II trials.

2.4.1. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose finding studies

Dose-finding was done in two double-blind, randomized, placebo controlled clinical trials in two appropriate pain models. In these trials, study medication was administered by study personnel and not the PCA System. This was considered acceptable with regard to the objective of dose finding, as the manual dispensing of trial medication ensured that no device malfunction could interfere with treatment.

Pivotal phase III studies IAP310 and IAP311

The selected patient population for trials IAP310 and IAP311 was considered appropriate. Major orthopaedic surgery and major abdominal surgery are accepted pain models for postoperative moderate to severe musculoskeletal and visceral pain, respectively. The primary endpoint was time-weighted SPID measured after 48 hours and patients had the option to continue in the trials up to72 hours after start of medication.

The primary endpoint was defined as difference to baseline and time-weighing to account for the varying assessment-intervals was supported by the CHMP. The chosen definition assumed that the pain intensity has been present immediately after the previous measurement. This was an unrealistic assumption and overestimated the pain decrease, as pain after surgery has a tendency to decrease only gradually. In consequence, a treatment arm with a larger retention rate received a reward compared to a treatment arm with a larger drop-out rate, where the last pain assessment was carried forward (LOCF). As more patients on placebo dropped out, the investigational treatment was favoured. This also applied to the BOCF and WOCF analyses and thus these might have replicated the primary analysis. Regarding both issues, conservative analyses, which do not penalize the placebo treatment arm more than the sufentanil arm were requested by the CHMP. In response, the applicant performed sensitivity analyses considering measured pain intensities to be representative for the subsequent intervals as well as imputation of missing data using a multiple imputation approach sampling from placebo data. Both analyses demonstrated that a robust treatment effect was also shown with more conservative assumptions in both trials. This was in line with other analyses, like the frequency of drop-outs and the need for rescue medication, which are not affected by data imputation and which show positive results for Sufentanil.

Furthermore, the predefined analysis outcome for the primary endpoint was difficult to interpret, as the SPID is by definition larger the longer the observation interval is. Rescaling by dividing the weighted SPID by the length of the observation period was requested as an additional analysis. This resulted in an average pain reduction over the time-period, which allowed for an easier interpretation with reference to the original scale, as well as comparison between time-points. The submitted results showed that a clinically relevant treatment effect was achieved over all time-points in both pivotal placebo-controlled trials.

Despite the methodological weaknesses inherent to the primary endpoint, the CHMP concluded that the pivotal trials provide sufficient evidence of efficacy of Zalviso in post-operative pain. The secondary endpoints that allow for assessment of clinically relevant outcomes (e.g. proportion of patients who terminated due to inadequate analgesia, proportion of patients requiring rescue medication, total amount of supplemental and rescue medication) were considered able to compensate possible shortcomings of the primary endpoint.

The results for the 72hrs time-point remained difficult to interpret as the patients could opt either to continue or leave the trial after the 48hrs assessment. The individual reason for the patient decision was not collected, therefore the estimates for the 72hr time point may be unreliable and even biased, and consequently need to be interpreted with caution.

Trial IAP309

A third phase III trial, a randomized, open-label non-inferiority trial versus IV morphine pump PCA, tested the efficacy of Zalviso against the current gold standard for the management of acute post-operative pain. Patients after hip or knee replacement or open abdominal surgery were enrolled; the primary endpoint in this study was patient global assessment of the method of pain control at 48 hours.

Despite the open-label design, an interim analysis for sample size reassessment has been performed. This was considered problematic, as this approach can lead to considering the effect size even unintentionally, although no apparent adaptation has been performed by the Applicant.

No acceptable justification for the non-inferiority margin of 15% was provided and the margin was considered to be large. Also, due to its categorical outcome, the primary endpoint for study IAP309 was not sensitive to detect differences between the treatments, i.e. it facilitated the conclusion of non-inferiority. Furthermore, the strength of the subjective patient-assessment of this endpoint, both in the open-label setting as well as in view of the non-inferiority design, remains uncertain.

As this trial was performed in addition to two pivotal double-blind trials and showed superior effects to morphine, and not only non-inferiority as originally planned, the CHMP agreed that it can be accepted in supportive evidence for efficacy of Zalviso. In summary, the convincing results of this trial were able to outweigh the methodological concerns.

All Phase III trials were multi-centre and conducted in the US. There are no substantial differences between Europe and the United States in pain management practices; therefore the CHMP considered that it was possible to extrapolate the results from the US setting to the European population.

Efficacy data and additional analyses

The primary efficacy endpoint in the phase II trials was the time-weighted sum of pain intensity differences at 12 hours (SPID12), in the phase III trials the time-weighted sum of pain intensity differences at 48 hours (SPID48). Although SPID is an accepted endpoint in pain trials, according to the available draft guideline (EMA/CHMP/970057/2011), pain scores are probably not best suited to the evaluation of acute postoperative pain because the objective of treatment is the best possible relief of pain.

Nevertheless, the primary endpoint in every trial was consistently statistically significantly different from placebo and is supported by secondary endpoints. Of these “termination due to inadequate analgesia” was considered to be of special relevance for the evaluation of the analgesic efficacy of sublingual sufentanil.

The analgesic efficacy of the 15 µg sufentanil dose used in Zalviso was shown consistently across the phase II trials and phase III trials. In addition, sufentanil is not a new active substance, but has been in use for decades for pain control during surgical procedures and as an analgosedative agent in intensive care treatment in its intravenous presentation.

In view of the rather high rates of rescue medication and supplemental morphine use documented in the phase III trials the applicant was asked to provide a comparison with other trials in postoperative (patient controlled) analgesia in order to justify and put the observed rates into perspective. Regarding the rates of rescue morphine use, the Applicant presented data from trials with a comparable analgesic (fentanyl)/ device combination for PCA developed for the same indication as Zalviso. Due to inherent differences in trial design, outcomes are not directly comparable. However, the use of rescue medication reported in the first three hours of these trials was also high (45%, 48% and 34%).

In addition, the Applicant summarized published data from double blind, placebo controlled clinical trials in postsurgical pain. Of special relevance are those identified trials that use an opioid as the test product, i.e. hydroxycodone, tapentadol and extended release epidural morphine. Taking into account different observation periods and different trial designs, the rates of rescue medication use observed in the Zalviso pivotal trials appear comparable or even lower than those observed with other opioid agents. Concerning the use of supplemental morphine, a comparison to the observed rates in a comparable analgesic/device combination was provided. Additionally, the impact of the high dropout rate in the placebo arms together with a high placebo effect in trials of analgesic substances on the use of supplemental morphine for the

phase III trials was discussed. In summary, the provided external comparisons and justifications are reassuring with regard to the rates of rescue/supplemental morphine in the Zalviso programme.

The originally proposed indication "Zalviso is indicated for the management of moderate to severe acute pain" was not accepted by the CHMP. In the submitted clinical trials Zalviso has been investigated in post-operative pain only. However, the applicant claimed that positive confirmatory trials in 2 surgical pain models, covering both somatic and visceral pain, can be extrapolated to other acute pain conditions in general, in accordance with the provisions in the relevant Guideline (EMA/CHMP/970057/2011). In the CHMP view such an extrapolation could not be made from postsurgical pain models to other acute pain conditions in this specific case. Installing and using the device require a considerable time-frame, therefore the setting would not be appropriate for occasional use and not appropriate when prompt and marked effect is required e.g. biliary or renal cholic pain or pain from myocardial infarction. Similarly, extrapolation is not considered appropriate from postsurgical models to breakthrough pain because cancer patients who experience breakthrough pain are still on opioid treatment and may therefore require higher sufentanil doses. It should be also noted that breakthrough pain is paroxysmal and the time needed to reach effective analgesia was not sufficiently rapid with low doses of sufentanil. Additionally, PCA targets generally the minimal effective concentration, which is expected to be insufficient to control a suddenly increased pain.

In summary, although opioids in general and sufentanil in particular are effective analgesics in various pain conditions, the limitations in the dose, the fixed minimum dosing interval inherent to PCA with Zalviso and the onset of effect preclude granting a general acute pain indication for Zalviso. Therefore, the CHMP recommended that the indication should be restricted to postoperative pain only.

The CHMP noted that as the doses of sufentanil as well as the lock out interval of 20 minutes are fixed, it could potentially lead to underdosing and thus lack of efficacy in large or obese subjects. An additional analysis of the primary and relevant secondary endpoints by body mass index (BMI) categories (<30, 30 to <40, and ≥40) was requested. For the BMI categories below 40, there was a consistent positive effect observed in favour of sufentanil on the primary (SPID48) and other secondary endpoints in both pivotal trials. For the highest BMI category (⩾40) in IAP310, the results are consistent with the other BMI categories. However, in IAP311, there was an inconsistent trend for this category, driven by the significantly greater placebo response, the imbalance in the number of subjects by surgery type, and the small number of subjects in the placebo group. Due to the reasons this outcome cannot be unequivocally interpreted.

2.4.2. Conclusions on the clinical efficacy

The results of the Phase III program demonstrate that Zalviso is an efficacious and convenient method for patient controlled analgesia in the post-operative setting.

2.4.3. Clinical safety

Patient exposure

The overall exposure data are summarised in Table 23 below.

Table 23 Overall sufentanil sublingual tablet exposure

Trial identifier	Phase	Population studied/ Trial type	Total number of subjects exposed to any SST dose [a]
Phase I trials	I	Total Phase I trials	153 [b]
ARX-C-001	II	In-patients with acute pain/ RDBPC (12-hour treatment period)	70 [c]
ARX-C-004	II	In-patients with acute pain/ OL (12-hour treatment period)	30
ARX-C-005	II	In-patients with acute pain/ RDBPC (12-hour treatment period)	58 [c]
Total Phase II trials			158
IAP309	III	In-patients with acute pain/ OL, active comparator (up to 72 hours of treatment)	177
IAP310	III	In-patients with acute pain/ RDBPC (up to 72 hours of treatment)	114
IAP311	III	In-patients with acute pain RDBPC (up to 72 hours of treatment)	315
Total Phase III trials			606
OVERALL TOTAL subjects enrolled: SSTS 5, 10, or 15 µg			917 [d]
OVERALL TOTAL in-patients exposed to proposed to-be-marketed dose: SSTS 15 µg			685 [e]

a) This number includes subjects exposed to any dose of SST. Many of the PK trials were of crossover design and therefore, the enrolled subjects in these trials may have received a different dose of SST on separate days.

b) Of 153 healthy adults in these trials, 105 were naltrexone-blocked.

c) In trial ARX-C-001, there were 24 subjects who received a 5 µg dose and 26 who received a 10 µg dose. In Trial ARX-C-005, there were 29 subjects who received a 10 µg dose.

d) All SST exposure, including subjects in Phase I trials who were naltrexone-blocked and subjects in Phase II trials who received SSTS doses of 5 and 10 µg.

e) n = Subjects exposed to SSTS 15 µg in Phase II and Phase III trials.

OL = open-label; PC = placebo-controlled; PK = pharmacokinetic; RDBPC = randomized, double-blind, placebo-controlled; SST = sufentanil sublingual tablet; SSTS = sufentanil sublingual tablet system.

Source: Mod2.7.4/Tab4.

709 patients received the sublingual tablet containing 15 µg sufentanil during the clinical trials program (phase I-III, naltrexone blocked phase I trials excluded). The duration of exposure in phase II and III trials was from ≥12 hours (544 patients) up to ≥72 hours (15 subjects).

Adverse events

In the Phase III, placebo-controlled trials most common adverse events were nausea (46.9% in the SSTS group and 36.4% in the placebo system group), pyrexia (17.7% versus 11.1%) and vomiting (11.7% versus 6.2%) headache (8.6% versus 8.0%), oxygen saturation decreased (7.7% versus 3.1%), pruritus (6.8% versus 0%), hypotension (5.6%versus 3.1%), dizziness (5.4% versus 1.9%), anaemia (5.1% versus 3.1%), constipation (5.1% versus 2.5%), and anaemia post-operative (5.1% versus 3.1%). In the open-label phase III trial IAP309, which compared directly SSTS with IV PCA morphine sulphate, the rates of common adverse events were similar.

Physical examinations in Phase II and Phase III trials included observations of the oral mucosa, as this is a potential source of AEs related to the new pharmaceutical form and route of administration. There were no adverse events of local irritation in any of the trials performed with the SSTS.

Serious adverse event / deaths / other significant events

There were two deaths during the clinical development program of the SSTS, both were considered unrelated to treatment.

There were few serious adverse events (SAEs) overall, and SAEs were consistent with opioid treatment and the post-surgical setting. Across all 3 Phase III trials, treatment-emergent SAEs (i.e., occurring during the treatment period and within 12 hours after discontinuation of trial medication) were experienced by 10 subjects (1.7%) in the SSTS group, 1 subject (0.6%) in the placebo system group, and 5 subjects (2.8%) in the IV PCA morphine sulfate group.

Across the Phase III trials, there was no clinically relevant difference in the occurrence of any SAEs among the SSTS, IV PCA morphine sulfate, and placebo system groups. Four subjects in the SSTS group experienced SAEs considered by the investigator to be possibly or probably related to treatment. These SAEs were oxygen saturation decreased (probably related), sinus tachycardia (possibly related), confusional state (possibly related), and respiratory depression (possibly related). Treatment was discontinued after the events of oxygen saturation decreased and sinus tachycardia. All of the treatment-related events resolved without sequelae.

Laboratory findings

There were no differences between treatment groups for mean changes from baseline for any laboratory variables. The majority of clinical laboratory values or changes were not considered clinically significant by the investigators. A number of subjects in each treatment group had changes in laboratory variables from below or within the normal range at baseline to above normal range at 48 hours or at the final evaluation. The proportion of subjects with such changes was similar for active and placebo group. These changes were as expected for a postoperative population (e.g., due to blood loss, volume depletion, dehydration or various concomitant medications) and were not considered to be clinically significant.

Some laboratory assessment results were reported as adverse events. In the 2 placebo-controlled, Phase III trials (IAP310 and IAP311), common adverse events (occurring in >1% of subjects) included anaemia (5.1%), hypoproteinaemia (4.0%), hypoalbuminaemia (3.7%), hypocalcaemia (3.5%), hypokalaemia (3.5%), hyponatraemia (1.9%), and hypomagnesaemia (1.2%). These adverse events were generally expected for this postoperative population.

No sufentanil-specific laboratory events were reported in this post-surgery population, no differences in treatment groups (SSTS, IV PCA morphine or placebo) could be detected.

Safety in special populations

Adverse events were summarized across integrated trial pools for the following subgroups: ages <65 and ≥65 years for all integrated trials and placebo-controlled, Phase III trials; ages 18 to <25, 25 to <65, 65 to <75, and ≥75 years for all Phase III trials; male and female subjects for all integrated trials and placebo-controlled, Phase III trials; Caucasian and non-Caucasian subjects for all integrated trials and placebo-controlled, Phase III trials; BMI <30, 30 to 40, and >40 kg/m2 for all Phase III trials and placebo-controlled, Phase III trials; and surgery type (knee surgery, non-knee surgery, hip replacement surgery, and abdominal surgery) for all integrated trials. Safety analysis across the different population subgroups showed consistency with the known risks of opioids.

Rates of adverse events tended to be higher in older subject groups and were higher in women than in men. However, there was no safety concern specific to any adult age group or for either sex.

As in the 2 placebo-controlled, Phase III trials, the overall rate of adverse events in all 3 Phase III trials decreased as BMI increased (from 83.6% to 78.1% to 74.1%) in subjects treated with the SSTS. In subjects treated with SST 15 µg, the rate of adverse events was higher in knee surgery than non-knee surgery subjects and lowest in subjects who underwent abdominal surgery. However, these differences were not judged to be clinically significant.

Adverse events were also summarized for placebo-controlled, Phase III trials by severity of hepatic or renal dysfunction (normal function or mild, moderate, or severe dysfunction). There was no specific safety concern identified related to the treatment of subjects with sufentanil who had various degrees of hepatic or renal impairment. However, no firm conclusions can be drawn due to the small number of subjects with hepatic or renal impairment enrolled in the trials.

Safety related to drug-drug interactions and other interactions

Ketoconazole, a potent CYP3A4 inhibitor, can increase the systemic exposure to sublingual sufentanil as shown in phase I study IAP104 described in the Pharmacokinetics section. The increased area under the curve (AUC) caused by concomitant administration of CYP3A4 inhibitors will prolong the analgesic effects and, as a result, the inter-dosing interval could increase. However, the clinical relevance of this effect is small as the variable inter-dosing interval of the SSTS should compensate for the increased AUC caused by concomitant administration of CYP3A4 inhibitors.

As sufentanil is a well-known substance, other clinical interactions are known and described in published literature. Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when sufentanil is administered to patients receiving barbiturates, tranquilizers, other opioids, general anaesthetic or other CNS depressants. In such cases of combined treatment, the dose of sufentanil and/or these agents should be reduced. The use of benzodiazepines with sufentanil during induction may result in a decrease in mean arterial pressure and systemic vascular resistance. All relevant historical data have been adequately reflected in the Product Information.

Discontinuation due to adverse events

Across all Phase II and Phase III trials, 6.9% of subjects in the SST 15 µg group, 11.1% in the IV PCA morphine sulfate group, and 6.0% in the placebo system group experienced adverse events leading to discontinuation.

2.4.4. Post marketing experience

No post-marketing data are available with sufentanil SSTS since the medicinal product has not been marketed in any country. However, there is large experience with sufentanil in other pharmaceutical forms and in other indications since its first authorisation in 1978.

2.4.5. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The safety assessment in this application has been based on historical data from the active substance sufentanil and clinical study data (phase I-III) provided by the Applicant. The main and clinically relevant differences between Zalviso and licenced sufentanil products are the new dosage form, the application via dispenser (SSTS), the new indication and the administration via PCA; all these factors have been evaluated with regards to the safety profile.

Studies not conducted with the final delivery system have been regarded by CHMP as supportive only as the use of the product in clinical practice was not adequately reflected. This applied to phase II studies using sufentanil doses <15 µg as well as PK Studies using naloxone.

The CHMP noted that, when administered intravenously, sufentanil shows an AE profile quite similar to other opioids and systemic side effects are believed to be similar with the sublingual formulation as well. Medical experience with post-operative administered opioids (e.g. the closely related fentanyl or morphine) is large in general; the side effects due to the secondary pharmacology are known and well understood. Most common opioid adverse events such as gastrointestinal disorders, respiratory depression and nervous system disorders were also reported in trials conducted with Zalviso. Rates and quality of common adverse events and treatment related adverse events were as expected, with nausea being the most prominent. In placebo-controlled, Phase III trials, treatment-related adverse events were experienced by 198 subjects (46.2%) in the SSTS group and 50 subjects (30.9%) in the placebo system group. The rate of subjects experiencing at least 1 adverse event for SST was generally higher than placebo in key trial pools, but lower than IV PCA morphine sulphate. No relevant dose-dependent increase in AE rates was seen comparing the three different doses tested in phase II studies, 5mcg, 10mcg and 15mcg. Overall, the CHMP concluded that reviewed data suggest no aberrations from the well-known opioid safety profile.

The Applicant has originally proposed that Zalviso can be administered in "medically supervised environment". However, because sufentanil has pronounced sedative properties, potentially leading to respiratory depression, in addition to a high addictive potential, the CHMP recommended that its use should be restricted to in hospital use where quick access to appropriate medical intervention is available. This has been clearly stated in section 4.2 of the SmPC: "Zalviso is to be administered in a hospital setting only ".

The CHMP noted that the majority of patients (n= 613) was observed until 48 hours after treatment start, and only a limited proportion of patients (n=138) continued to the 72 hours mark. Moreover, postsurgical pain is a type of pain that improves without intervention with the passage of time and can be managed with non-opioid analgesics after the initial postoperative phase. Weaning from opioids was considered especially important with regards to the unwanted effects on the GI tract (i.e. ileus, constipation, which are of special relevance after abdominal surgery) and with regards to the addictive potential of opioids. In addition, the transition to analgesics with a longer half-life is important from a patient perspective, as a frequent intervention that is necessarily made by the patient due to the short half-life would interfere with adequate rest and recuperation time.

Therefore, the CHMP considered necessary to limit the recommended maximum duration of administration to 72 hours.

Although sufentanil safety is well established in higher doses when administered by the intravenous route, the time of administration is prolonged with the newly proposed indication. The possible impact on the safety profile cannot be ruled out as the risk for adverse events after reaching steady state is not only dependent on the dose level but also on the duration of exposure. As safety data for use of Zalviso at a maximum frequency (1 tablet 15 µg sufentanil every 20 minutes) were only available for a period of 13.3 h, the CHMP requested clarification on the maximum dose that could be reached for the maximum duration of use.

The CHMP acknowledged that it is highly unlikely that the maximal 72h dose will be reached in clinical practice. Patients sleep several hours or might be unable to use the device every 20 minutes due to post-operative care procedures or simply do not need such long lasting pain control. Results from phase III studies support this presumption; maximal allowed doses were not reached and the average time between doses over 48 hours of use was approximately 90 minutes. However, theoretically the applied dose could be about 1/3 higher than the maximum dose observed in phase III trials (216 vs 153 applications) and 5.7 fold higher than the average (216 vs. 38 applications).

A maximum frequency of use (40 repeated administrations of sufentanil 15 micrograms sublingual tablet every 20 minutes) yielded in a Cmax of 240 pg/mL which was still lower than that observed after a single IV dose of 15 µg (361 pg/mL) in 22 subjects in IAP102. However, the number of subjects in this Phase I study was rather limited and 13.3 hours do not reflect the maximum treatment duration.

Based on further pharmacokinetic and pharmacodynamic considerations, comparing sufentanil and other related morphine analogues, and taking into account available literature data for sufentanil exposure comparable with high-frequency Zalviso use up to 24hours, the CHMP concluded that no increased risk is expected if Zalviso is used highly frequently for the maximum permitted duration of 72 hours. However, section 5.1 of the SmPC has been updated to provide information about the dosing intervals and dosing frequencies of Zalviso during the phase III trials.

High doses not reached in the clinical trials could theoretically have an impact on local safety too. However, no harmful effects to the mucosa were reported in any of the trials (phase I-III). Furthermore, a local tolerance test in Golden Syrian hamsters showed no related local effects after 100 or 400 µg daily exposure with sufentanil for 4 days. An impairment of the local safety profile following administration of higher doses of Zalviso is therefore unlikely.

There was no specific safety concern identified by the Applicant in relation to the treatment of subjects who had various degrees of hepatic or renal impairment. However, the CHMP believed that no firm conclusions can be drawn due to the small number of subjects with moderate to severe hepatic or severe renal impairment enrolled in the trials and the population PK analyses, respectively. As sufentanil is primarily metabolized in the liver and excreted in the urine and faeces, the duration of action may be prolonged in patients with hepatic and renal impairment. Therefore, the CHMP recommended that Zalviso should be dosed with caution in these patients. Patients with severe renal insufficiency or moderate to severe hepatic impairment should be monitored carefully for symptoms of sufentanil toxicity. This information has been adequately reflected in the SmPC.

Safety and reliability of the sufentanil sublingual tablet system dispensing device

The safety and reliability of the medical device were not within the scope of the CHMP assessment. However, the medical device component is an essential element of the total system and indispensable to ensure the proper use of the medicinal product. Uncontrolled dosing due to failure of the device or application errors are an issue and could lead to inadequate doses – higher than needed (risk of side effects increased) or lower than needed (pain management impaired).

However, the non-invasive nature of SSTS may give rise to a somewhat heightened risk of misdosing (e.g., a patient misplacing the tablet or the tablet dropping onto the bed, which happened in very small numbers of cases in the trials). These risks have been addressed in the Risk Management Plan as device failure has been considered to be an important potential risk.

Abuse potential and Overdose

The abuse potential of sufentanil is well-characterized. The SSTS is designed to decrease the risk for misuse, abuse, and diversion of sufentanil and includes several security features to minimize the risk of intentional tampering and diversion. Provided that the SSTS functions properly, abuse precautionary measures seem adequate. As sufentanil is classified as narcotic, Zalviso will be subject to special medical prescription status.

Sufentanil is given via intravenous and epidural route in single doses up to 30-50 µg/kg body weight and in "continuous" doses up to 5 µg/kg/h (in single cases up to 15 µg/kg/h) in anaesthesia-settings according to EU SmPCs. An overdose with subligual sufentanil in adults as given via SSTS seems highly unlikely.

2.4.6. Conclusions on the clinical safety

The CHMP was of the opinion that the available safety data, including historical data for sufentanil authorised in other indications, supported the Application for Zalviso in the treatment of acute moderate to severe post-operative pain in adult patients. The safety profile was considered consistent with the post-operative setting and other opioid treatments, including IV PCA morphine sulphate. No suspected technical failure of the SSTS technology led to overdose, was associated with an adverse event, or led to the administration of more than a single sublingual tablet of sufentanil. The product information was amended to clearly reflect the mandatory use in a hospital setting and the maximum time of administration of 72 hours. Relevant safety data have been adequately reflected in the Risk Management Plan.

2.5. Pharmacovigilance

Pharmacovigilance system summary

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC. The applicant's pharmacovigilance system summary includes a reference to the location where the pharmacovigilance system master file for the medicinal product is kept and provides proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice with the request to update "device failure" as an important potential risk rather than important identified risk.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Important identified risks	Respiratory depression
	Hypersensitivity
Important potential risks	Drug abuse and drug diversion
	Off label use (including paediatric use
	Overdose
	Bradycardia
	Hypotension
	Paralytic ileus
	Spasm sphincter of Oddi
	Convulsions
	Use in patients with raised intracranial pressure
	Device failure
Missing information	Use in pregnancy
	Use during lactation
	Use in patients with hepatic and/or renal impairment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Activity: Effectiveness of the educational materials for HCP to ensure appropriate use of Zalviso and minimize risks to be evaluated with a surveyd. (Category 3)	1. To evaluate whether the educational materials have been provided to HCP through tracking distribution and documenting where training of the HCPs has been performed prior to use of Zalviso. 2. Assess whether HCP have followed the guidance provided in the educational materials through a survey in selected medical centers across EU countries 6 months to 2 years after launch (depending on market penetration and use of Zalviso).	Off-label use (including paediatric use), device failure and overdose	Planned	Outcome to be presented in PSURs according to PSUR submission timelines

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Respiratory depression (Important Identified Risk)	Contraindication in section 4.3 of the SmPC for patients with significant respiratory depression Warning in section 4.4 concerning increased risk of respiratory depression in patients with respiratory impairment or reduced respiratory reserve and that the degree/severity is dose related and that the use of antagonists can reverse respiratory depression caused by sufentanil Warning in section 4.5 concerning concomitant use of CNS depressants that may enhance respiratory depression Section 4.8 contains respiratory depression with a frequency of common (≥1/100 to <1/10). Warning in section 4.9 that respiratory depression may be an outcome of overdose Guidance in section 5.1 of the respiratory effects of sufentanil. A hospital setting is required for Zalviso administration and Zalviso should only be prescribed by physicians who are experienced, knowledgeable and skilled in the management of opioid therapy, particularly opioid adverse reactions such as respiratory depression. This will provide early detection and immediate management of respiratory depression if such a case occurs.	None proposed
Hypersensitivity (Important Identified Risk)	Contraindication in section 4.3 of the SmPC for patients with hypersensitivity to the active substance or to any of the excipients Warning in section 4.4 that Zalviso contains azo colouring agent sunset FCF (E110) which may cause allergic reactions Section 4.8 contains anaphylactoid shock and hypersensitivity with an unknown frequency and a frequency of uncommon (≥1/1,000 to <1/100) (based on IV administration of sufentanil) respectively. A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of hypersensitivity if such a case occurs.	None proposed
Drug abuse and drug diversion (Important Potential Risk)	Warning in section 4.4 of the SmPC about the potential for abuse. Sufentanil is a scheduled drug and is required to be administered in a hospital setting only. Prescription only medicine The sufentanil sublingual tablet system (SSTS) has in-built security features in place to prevent	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	overdose which make the abuse by the patient less convinient. These include a mechanically locked drug cartridge containing sufentanil tablets, a tether, an alarm, a priming cap with a unique optical signature, a patient ID thumb tag contains an RFID chip, an in-built 20 minute lock-out interval and in-built dose-tracking.	
Off label use (including paediatric use) (Important Potential Risk)	Guidance on indication in section 4.1 of the SmPC Guidance on use in paediatrics in section 4.2 Information on PK in paediatrics in section 5.2 Prescription only medicine A hospital setting is required for Zalviso administration.	Educational materials for healthcare professionals. The educational materials for HCP informing about the indication and how to appropriately select patients and use Zalviso according to the guidance in the SmPC to ensure appropriate use and minimize risks.
Overdose (Important Potential Risk)	Guidance on posology in section 4.2 of the SmPC Guidance on overdose in section 4.4 in patients with severe renal or hepatic impairment Warning in section 4.9 about the risk of overdose and outcome and treatment Prescription only medicine A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of overdose if such a case occurs. Zalviso is administered as a single fixed dose of 15mcg sufentanil sublingual with a 20 minute lock-out period between doses.	Educational materials for healthcare professionals. The educational materials for HCP inform about the indication and how to appropriately select patients and use Zalviso according to the guidance in the SmPC to ensure appropriate use and minimize risks.
Bradycardia (Important Potential Risk)	Warning in section 4.4 of the SmPC about the risk of bradycardia and to advise caution in patients with previous or pre-existing bradyarrhythmias. A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of bradycardia if such a case occurs.	None proposed
Hypotension (Important Potential Risk)	Warning in section 4.4 of the SmPC about the risk of hypotension and to advise caution in hypovolemic patients A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of hypotension if such a case occurs.	None proposed
Paralytic ileus (Important Potential Risk)	Warning in section 4.4 of the SmPC about the risk of paralytic ileus and to apply caution in patients at risk of ileus A hospital setting is required for Zalviso	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration. This will provide early detection and immediate management of paralytic ileus if such a case occurs.	
Spasm sphincter of Oddi (Important Potential Risk)	Warning in section 4.4 of the SmPC about the risk of spasm of sphincter of Oddi and to advise caution in patients with biliary tract disease including acute pancreatitis. A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of spasm sphincter of Oddi if such a case occurs.	None proposed
Convulsions (Important Potential Risk)	Convulsions is listed as an adverse reaction in section 4.8 of the SmPC. A hospital setting is required for Zalviso administration. This will provide early detection and immediate management of convulsions if such a case occurs.	None proposed
Use in patients with raised intracranial pressure (Important Potential Risk)	Warning in section 4.4 of the SmPC regarding the use of Zalviso in patients with raised intracranial pressure, impaired consciousness or with brain tumours. A hospital setting is required for Zalviso administration with prescription by a healthcare professional. This will limit the use of Zalviso in patients with raised intracranial pressure.	None proposed
Device failure (Important Potential Risk)	The HCP will be provided with Instructions for Use Guide with a detailed description of the device failures and actions to take in case of their occurrence. A hospital setting is required for Zalviso administration. This will ensure quick detection of device failure, limiting the poitential therapeutic gap and early detection of a potential overdose or other sufentanil adverse reaction.	Educational materials for healthcare professionals. The educational materials for HCP inform about the indication and how to appropriately select patients and use Zalviso according to the guidance in the SmPC to ensure appropriate use and minimize risks.
Use in pregnancy (Missing Information)	Guidance in section 4.6 of the SmPC Prescription only medicine	None proposed
Use during lactation (Missing Information)	Guidance on use during lactation in section 4.6 of the SmPC Prescription only medicine	None proposed
Use in patients with hepatic and/or renal impairment (Missing Information)	Guidance in 4.2 of the SmPC and a warning in 4.4 to apply caution when administering Zalviso to patients with hepatic and/or renal impairment. A hospital setting is required for Zalviso administration with prescription by a healthcare professional. This will ensure timely detection of	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	ADRs by HCPs should they occur. Prescription only medicine	

2.6. Product information

2.6.1. 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.

2.6.2. Labelling exemptions

A request to omit certain particulars from the labelling 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:

The medicinal product is prone to oxidation and hence is kept sealed with an oxygen absorber in an air-tight sachet. The expiry date is only valid while the cartridge is sealed within its sachet. A printed expiry date on the cartridge label may lead to confusion and may mislead the healthcare professional to store the cartridge outside the sachet for the stated shelf life. The outer carton as well as the sachet contain the information to the healthcare professional to place the cartridge immediately into the administration device after removal from sachet to prevent such case.

Therefore, the QRD Group accepted the exemption request to not print the expiry date on the cartridge label on the basis of article 63.3 based on its special storage conditions.

The particular (expiry date) will be omitted from both the printed materials and the published Annexes in order to avoid any confusion with regards to the storage conditions of the cartridge (to be kept in sachet until ready to use).

3. Benefit-risk balance

Benefits

Beneficial effects

Zalviso contains 15 µg sufentanil in a new sublingual form. Sufentanil is reliably resorbed from the sublingual space. The uptake of sufentanil occurs more gradually over time resulting in a context-sensitive half-life (CST½, i.e. time from C_{max} to 50% of C_{max}) of about 2 hours compared to a CST½ of 8 minutes after intravenous administration, which provides a more appropriate duration of analgesia in the setting of patient controlled analgesia.

The analgesic properties of the Zalviso Nano Tab system were tested in the management of acute post-operative pain after open abdominal or knee/ hip replacement surgery. Patients self-administered the 15 µg sufentanil tablet with a dedicated hand-held device with a lockout interval of 20 minutes. The

population included in the clinical studies is considered representative of post-operative patients in the hospital setting, including a sufficient number of elderly patients.

In the two pivotal randomised, double blind, placebo-controlled phase III trials of similar design, the primary endpoint (time-weighted SPID48) was consistently statistically significantly different from the effects of placebo: 105.60 vs. 55.58 in IAP310; 76.24 vs. -11.35 in IAP311. In addition, all clinically relevant secondary endpoints were in favour of sufentanil, e.g. termination due to inadequate analgesia (IAP310: 17.4% vs. 31.6%; IAP311: 14.3% vs. 48.1%) or use of rescue medication (IAP310: 33.0% vs. 66.7%; IAP311: 50.8% vs. 73.1%).

A third phase III, open-label trial studied non-inferiority of Zalviso PCA versus IV morphine PCA, which is the gold standard for the control of postsurgical pain. The Zalviso Nano Tab system showed superiority for the primary endpoint, patient global assessment of the method of pain control at 48 hours (IAP309: 78.5% vs. 65.6% of patients who responded “good” or “excellent”). All secondary endpoints were in favour of the sufentanil system over the morphine pump. In addition, scores for Zalviso were superior to those for the morphine IV pump in the healthcare professional global assessment and the patient ease of care questionnaire.

The clinical relevance of the achieved effect in pain reduction with Zalviso is supported by responder analyses conducted in line with literature recommendations (IMMPACT). According to these publications, a 30% pain reduction indicates at least moderate clinically important differences and a 50% reduction correlates with substantial improvements. The responder analyses from the pivotal trials IAP310 and IAP311 show that a 30% reduction was achieved in 60% and 55%, respectively, of patients in the Zalviso group versus 37% and 25% of patients in the placebo group. A 50% pain reduction was reached in 37% and 31% of Zalviso patients in these trials as compared with 17.5% and 9.6% of placebo patients.

A potential benefit of the product lies also in the route of administration: sublingual tablets do not require intravenous access, and thus, all the problems inherent to IV administration of medicinal products can be avoided. This benefit also includes greater mobility of the patients, as they do not need to be tethered to an infusion device in order to control their pain, although this might be less relevant in the immediate post-operative period. Programmable pumps, sensitive in matters of handling and dosing errors, can be avoided.

Uncertainty in the knowledge about the beneficial effects

For the double-blind trials IAP310 and IAP311, a statistically significant treatment effect is considered to be demonstrated. Initially, several methodological aspects of the primary endpoint and its predefined analysis imposed some uncertainty on the actual extent of the effect size and on the interpretation of the primary analysis result. This referred to difficulties in interpretation of a sum score of pain reduction, but also to aspects relating to the calculation of the sum score. In addition, several assumptions, including missing data imputation appeared to favour treatment with Zalviso. These concerns have be resolved with requested additional analyses. However, the fact that decision on study continuation after the 48hrs period was selective and data based remains, rendering the results for the 72hrs time point difficult to interpret.

Some uncertainties remain for study IAP309. Though the study had an open-label design, an interim analysis for sample size reassessment was performed, and even if no apparent adjustment was made, the study conduct could have been influenced by considering the treatment effect. Furthermore, the categorical primary outcome was not sensitive and facilitated conclusion of non-inferiority. The strength of the subjective patient-assessment of this endpoint remains uncertain in the open-label setting. No acceptable justification was given for the chosen non-inferiority margin of 15%, which is considered to be

large. However, as superiority against morphine was shown as the primary endpoint, in the CHMP opinion this outweighs methodological concerns.

The rates of rescue medication and supplemental morphine use in the phase III trials were considered rather high. A comparison with other trials in postoperative PCA was considered relevant to justify and put the observed rates into perspective. Data from trials with a comparable analgesic (fentanyl)/ device combination for PCA developed for the same indication as Zalviso show that the use of rescue medication in the first three hours of these trials was high (45%, 48% and 34%). In addition, published data from double blind, placebo controlled clinical trials in postsurgical pain were considered; trials using an opioid as the test product, i.e. hydroxycodone, tapentadol and extended release epidural morphine, being of special relevance. Acknowledging differences in study periods and trial designs, the rates of rescue medication use observed in the pivotal Zalviso trials appear comparable or even lower than those observed in studies with other opioid agents (Daniels et al. 2011; Gambling et al. 2005). Moreover, high dropout rates in the placebo arms of the pivotal trials as well as a substantial placebo effect in trials of analgesic substances in general, impacting on the use of supplemental morphine in the phase III trials, have to be taken into account. In summary, the provided external comparisons and justifications are reassuring with regard to the rates of rescue/supplemental morphine use in the Zalviso programme.

There was a trend towards higher SPID48 scores in females versus males and in patients with a lower body mass index versus those with a higher BMI in the pivotal phase III studies. Additional analyses demonstrated consistent beneficial findings for sufentanil in most subgroups. However, in IAP311, there was an inconsistent trend for the high BMI category, apparently driven by the significantly greater placebo response, the imbalance in the number of subjects by surgery type, and the small number of subjects in the placebo group.

In the active controlled phase III trial (IAP309) the percentage of subjects who experienced an oxygen saturation decrease to below 95% was lower in the Zalviso group than in the IV PCA morphine sulfate treatment group (20% versus 30%, p=0.028), and numerically fewer patients had values below 94% and 93%. However, differences between groups for mean change from baseline in oxygen saturation were generally not statistically significant or considered not clinically meaningful. The signal was only seen in one study, and the total number of patients is limited.

Sublingual administration of the Zalviso NanoTab harbours the risk of misplacement of the tablet that might not be recognized by the patient, because the tablet is very small, tasteless and melts without noticeable effect. This is less problematic if the NanoTab is placed somewhere else on the oral mucosa, but it can be the reason for a putative treatment failure if the tablet is swallowed, because of the very low oral bioavailability of sufentanil.

Risks

Unfavourable effects

Risks associated with Zalviso are predominantly in line with the well-known class effects of opioids, including the adverse event profile and the abuse potential.

The known sufentanil related side effects were seen in clinical trials conducted with Zalviso. The most frequent AEs were (in descending order) gastrointestinal events, neuropsychiatric events and respiratory events. Nearly 30% of patients experienced treatment-related nausea in the placebo controlled phase III trials. 6.1% (vs. 2.5% for placebo) of subjects suffered from treatment related decreased oxygen saturation, which is of special interest in this vulnerable, post-surgery patient population. These effects necessitated the restriction of use of the Zalviso system to a hospital environment, where these

potentially life threatening events can be recognized and controlled in a timely manner. In addition, Zalviso has been contraindicated in patients with significant respiratory depression.

The comparison with morphine, which is the gold standard in the targeted indication, showed similar safety profile of both treatments, with no obvious disadvantages of the SSTS.

Sufentanil abuse could occur due to improper handling of the device or by individual choice, exploiting the PCA mode of administration. This is, however, not very likely due to the nature of the administration in a hospital environment and the safety features of the device.

Uncertainty in the knowledge about the unfavourable effects

Uncertainty lies within the new mode of application, administration as PCA and a new therapeutic indication.

The delivery system has obtained a CE mark from the Notified Body; hence, its technical function is certified. However, as it is new and has not demonstrated its reliability and practicability in the broad clinical setting, it is a source of uncertainty at the moment.

PCA could trigger unknown effects on different levels; patients as well as medical staff might not be capable (or willing) of handling the device properly and treatment errors could occur. This can be attenuated by accurate instructions in the PI, proper introduction and training given with the device and by gaining experience over time. No cases of overdosing were observed in the clinical development and the device features should prevent overdosing given the 20min lock-out period.

The new therapeutic indication introduces sufentanil in the postoperative setting with prolonged use compared to already licensed sufentanil products. Approximately 700 patients received Zalviso through the final to be marketed device, so the experience with this product is currently limited. However, as this is a hybrid application, historical data from other sufentanil products were considered to be supportive for this evaluation.

Some uncertainty arises with regards to the safety of the maximum dose in the 72hrs dosing period, as this was never reached in any of the clinical trials. In fact, patients rarely used Zalviso at the maximal frequency for more than 12hrs. The discussion provided including pharmacokinetic and pharmacodynamic considerations, comparing sufentanil and other morphine analogues, indicates that no increased risk is expected if Zalviso is used at high/maximum frequency for the permitted duration of 72 hours. Overall, taking into account the provided clinical and historical data, the impact of these uncertainties seems to be rather small.

Balance

Importance of favourable and unfavourable effects

The beneficial effects of a patient controlled analgesia option which does not necessitate an intravenous access and thus avoids the well-known problems of IV administration, including restricted mobility and potential handling and medication errors, are considered to be relevant and beneficial to a large population of patients who have to undergo major surgery.

The observed unfavourable effects seem to be comparable to those of the current gold standard PCA option, which uses morphine as the analgesic agent. These effects are inherent opioid class effects, like

gastrointestinal discomfort and respiratory depression, and medical staff is familiar with managing these complications on the ward.

Benefit-risk balance

Given the practicability of the new mode of administration, the good bioavailability and the resulting rather stable serum concentration of the active substance, the SSTS appears to present a welcome improvement in PCA, even if the sublingual administration harbours the risk of misplacement of the tiny Nano tablet resulting in lack of effect and insufficient analgesia.

Zalviso is considered to be a user-friendly product (for patients and medicinal staff) with good analgesic properties that performed as good as the gold standard (i.e. IV morphine) in post-surgery pain treatment, with regards to safety and efficacy. The availability of several treatment options is crucial for health care providers as they offer flexibility and enhance possibilities to individualise treatments. Therefore CHMP concluded that the benefit/risk balance of Zalviso in the treatment of acute post-operative pain is positive.

Discussion on the benefit-risk assessment

Establishing another option for patient controlled analgesia is considered meaningful for patients and healthcare professionals alike. Especially in the initial post-operative period, where surgical pain is worst, the benefits of Zalviso are considered clinically significant. However, post-operative pain is self-improving over time. In addition, timely weaning from opioids is considered especially important with regard to unwanted effects on the GI tract (e.g. ileus, constipation); together with the possibility of development of tolerance to sufentanil after continuous use over 72 hours and given its addictive potential, the benefit risk balance becomes less positive over time. Thus, a restriction of the maximum duration of use to 72 hours reflecting the experience from the three phase III trials was implemented. Moreover, with regard to the efficacy and safety of the product, a restriction of the indication to treatment of post-operative acute pain and use in the hospital setting was warranted. More experience with the device is needed before a broader use in a less strictly supervised environment could be considered.

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 Zalviso in the treatment of acute moderate to severe postoperative pain is favourable and 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).

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Zalviso is launched all healthcare professionals who are expected to prescribe Zalviso are informed through an information letter on having access to / are provided with the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational materials for the healthcare professionals

The Educational material shall contain the following key messages:

- Inform about the indication and how to appropriately select patients;
- Use Zalviso according to the guidance in the SmPC to ensure appropriate use and minimize risks.

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

Not applicable.