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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Exparel liposomal

International non-proprietary name: bupivacaine

Procedure No. EMEA/H/C/004586/0000

Note

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



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List of abbreviations

ASMF	Active Substance Master File = Drug Master File
BET	Bacterial endotoxin testing
BSA	Bovine serum albumin
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CQA	Critical Quality Attribute
DEPC	Dierucoylphosphatidyl choline
DPPG	Dipalmitoylphosphatidylglycerol
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
FDA	Food and Drug Administration
ETFE	Ethylenetetrafluoroethylene
FTU	Flip-tear-up
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IVR	In vitro release
MVL	Multivesicular liposome
PBS	Phosphate buffered saline
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
PPV	Packed particle volume
QP	Qualified person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
USP	United States Pharmacopoeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PACIRA IRELAND LIMITED submitted on 24 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Exparel liposomal (referred to as Exparel throughout this document), 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 15 September 2016. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication “for *prolonged acute pain management and reduction in need for opioids in adults compared to immediate release (IR) bupivacaine*”.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0036/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000877-PIP03-17-M01 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Natalja Karpova Co-Rapporteur: Margareta Bego

The application was received by the EMA on	24 May 2019
The procedure started on	20 June 2019

The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 September 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 September 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 September 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 April 2020
The CHMP agreed on a List of Outstanding Issues to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 September 2020
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 Exparel on	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Acute and chronic pain control is a significant clinical challenge. Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. According to the Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011) pain can be described as acute or chronic according to its duration. Acute pain is considered adaptive, in that it has a warning function. It is of short duration (generally up to a few weeks) and declines with the healing of the underlying injury or disease (e.g. post-surgical pain). Pain after surgery is a predictable part of the postoperative experience. Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction and initiation of an afferent neuronal barrage. However, like all pain, postoperative pain is complex and multidimensional. Postoperative pain control is an essential component of the care of the surgical patient.

2.1.2. Epidemiology

A study of 56 World Health Organization member states estimated that annually 234.2 million major surgical operations take place worldwide (95% CI 187.2–281.2 million). This translates into about one surgery each year for every 25 people. Surgery induces important disturbances in body homeostasis such as hypercatabolism, hypercoagulability, and inflammation, leading to a series of symptoms and signs such as hypoxaemia, pain, nausea, vomiting, ileus, sleep disturbances, and fatigue, and complications including pneumonia and myocardial infarction. Postoperative pain is often the predominant symptom.

According to the applicant, approximately three in four patients who experience acute postoperative pain report it as moderate, severe, or extreme in intensity (Apfelbaum 2003; Gan 2014). More than 80% of patients who undergo surgical procedures experience acute postsurgical pain (PSP) and approximately 75% of those with postoperative pain report the severity as moderate, severe, or extreme (Chou, 2016). The incidence of severe PSP, with significant functional deficit is estimated at 5-10%, and effective approaches to prevent it are basically ignored (Sansone, 2015). During the postoperative period, pain manifests itself with maximum intensity during the first 24 hours, reducing progressively (Nava-Obregón, 2016). Therefore, the onset of postoperative pain treatment requires a timely and efficient treatment, keeping in mind that it may extend to up to a week.

Postoperative pain remains an important problem despite notable advances in the scientific understanding of pain in recent decades. Poor management of postoperative acute pain may lead to the development of chronic pain. This occurs in 10%–50% of patients after various common operations. Once pain has become chronic, it is generally regarded as maladaptive and difficult to treat as patients’ response to currently available treatments is highly variable. Multiple and complex mechanisms are frequently involved, including somatic, psychological and socioeconomic factors. Associated disorders such as depression, anxiety and sleep disturbances may have an additional impact (Guideline on the clinical development of medicinal products intended for the treatment of pain; EMA/CHMP/970057/2011). Prevention of chronic postsurgical pain involves risk factors detection and evaluation, appropriate anaesthetic support and effective postoperative pain management. In addition to the significant personal suffering and social burden, postoperative pain has socio-economic consequences (prolonged hospitalisation, higher costs for care and treatment, re-surgeries, claims and compensations).

2.1.3. Aetiology and pathogenesis

Pain is a multifactorial condition involving multiple pathways. Acute pain in response to local tissue injury, such as surgery, is mediated through two basic systems: local pain receptors in the skin or organs and a local inflammatory response.

According to IASP website, acute pain after surgery has a distinct pathophysiology that reflects peripheral and central sensitisation as well as humoral factors contributing to pain at rest and during movement. Surgical tissue trauma leads to nociceptor activation and sensitisation. As a result, individuals suffer ongoing pain at rest and increased responses to stimuli at the site of injury. Different surgical procedures involve distinct organs and specific tissue within and adjacent to them, creating a variety of patterns of nociceptor sensitisation and differences in the quality, location, and intensity of postoperative pain. Mediators released locally and systemically during and after surgery that contribute to nociceptor sensitisation include prostaglandins, interleukins, cytokines and neurotrophins. Decreased tissue pH and oxygen tension, and increased lactate concentration, persist at the surgical site for several days. These responses may contribute to peripheral sensitisation and spontaneous pain behaviour following an incision. Nerves may be injured during surgery and hence discharge spontaneously. Spontaneous action potentials in damaged nerves may account for qualitative features of neuropathic pain that may be present early in the postoperative period and can evolve into chronic neuropathic pain. Noxious input during and after surgery can enhance the responses of nociceptive neurons in the CNS (central sensitisation) thereby amplifying pain intensity. The magnitude of central sensitisation depends on many factors, including the location of the operative site and the extent of the injury.

2.1.4. Clinical presentation, diagnosis

During the postoperative period, pain manifests itself with maximum intensity during the first 24 hours, reducing progressively (Nava-Obregón, 2016). According to the literature reference provided (Apfelbaum, 2003), most intense pain is experienced on postoperative day 1, which decreases slightly by postoperative day 3.

2.1.5. Management

Increasing evidence supports the use of multimodal analgesia to manage acute postsurgical pain (IASP, 2017; Garimella and Cellini, 2013). Systemic analgesics as components of multimodal analgesia used to treat postsurgical pain include (IASP, 2017): paracetamol, non-selective and cyclooxygenase-2 (COX-2), selective nonsteroidal anti-inflammatory drugs (NSAIDs), alpha-2-delta modulators (gabapentin, pregabalin), N-methyl-D-aspartate (NMDA)-receptor antagonists (ketamine), alpha-2 adrenergic agonists (clonidine, dexmedetomidine), systemic local anaesthetics, corticosteroids.

According to the applicant, local anaesthetics are particularly useful for management of moderate-to-severe acute pain and have been shown to improve postsurgical analgesia and reduce opioid utilisation (Allen 1998; Szczukowski 2004; Duarte 2006; Seet 2006; Good 2007; Paul 2010). Local anaesthetics may be used as a field block to create local analgesia around an injury, surgical site, or tissue plane or as a peripheral nerve block to create regional analgesia around a larger area. While conventional local anaesthetics are commonly used because of their long-standing benefit-risk profile, their duration of effect is typically shorter than the duration of moderate-to-severe postsurgical pain, which can often extend for several days.

Two primary treatment options to provide an extended duration of analgesia for moderate-to-severe pain are continuous peripheral nerve blocks or opioid analgesics. However, both treatment options come with clinical limitations:

- Continuous peripheral nerve blocks (CPNBs) require placement of a perineural catheter, local anaesthetic pump, infusion management, and catheter site care, which are technically

challenging and resource intensive. CPNBs carry risks for bacterial colonisation, infection, mechanical failure of the pump, catheter migration or dislodgement, wet bandages, and patient compliance issues (Jeng 2010; Joshi 2016).

- Opioid analgesics are associated with a high burden of opioid-related adverse events (ORAEs) such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, urinary retention, dysphoria, and delirium. ORAEs have been shown to increase hospital costs, increase lengths of hospital stay, impair patient outcomes, and increase the likelihood of readmission (de Boer 2013; Doan 2019; Kessler 2013; Oderda 2013; Shafi 2018). Management of ORAEs often requires the administration of additional medications including, but not limited to, antiemetics, anti-constipation agents, and anti-pruritus agents (Viscusi 2011).

Postoperative pain is not adequately managed in a significant proportion of patients and is associated with a broad range of negative consequences, including increased morbidity, development of chronic postoperative pain, impaired function, recovery from surgery, and quality of life, and prolonged opioid use (Gan, 2017). If pain is not controlled in the immediate post-operative period there may be several deleterious consequences such as delayed wound healing, extended hospital stay and the development of chronic pain syndromes (Macrae, 2001; Bonnet and Marret, 2005). Untreated or undertreated severe postoperative pain has many deleterious effects on respiration, circulation, autonomic activity, renal function, and gastrointestinal activity.

Inadequately managed acute postoperative pain is associated with effects related to aspects of both physiological and psychological function.

Changes can occur in diverse organ systems, including the cardiovascular (coronary ischemia, myocardial infarction), pulmonary (hypoventilation, decreased vital capacity, pulmonary infection), gastrointestinal (reduced motility, ileus, nausea, vomiting), and renal (increases in urinary retention and sphincter tone, oliguria) systems. A negative impact may also be seen on immune function, the muscular system, coagulation, and wound healing. Finally, poorly controlled pain after surgery may impair sleep and have negative psychological effects, such as demoralisation and anxiety. Unrelieved pain has considerable consequences as inadequate pain control post-operatively can result in increased morbidity and length of hospital stay and may lead to chronic pain (Raksamani, 2013).

Bupivacaine HCl is the current standard of care for post-surgical analgesia as one of the long-acting local anaesthetics, but even so it has a limited duration of action after local administration, usually reported as less than 8-12 hours (MARCAIN SmPC 2016).

2.2. About the product

Exparel is a prolonged-release liposomal dispersion of bupivacaine at a nominal concentration of 13.3 mg/mL.

Bupivacaine is one of the longer-acting local anaesthetics; thus, it is commonly administered to provide analgesia following surgery or a traumatic injury. However, the duration of action of IR bupivacaine is limited with a labelled duration of effect of up to 8 hours. Since moderate-to-severe acute pain following surgery or injury from trauma often lasts longer than the duration of action offered by current formulations of local anaesthetics, the rationale for developing Exparel has been to provide prolonged acute pain management via a single administration as a field block or peripheral nerve block.

Type of Application and aspects on development

This application has been submitted under Article 8(3) of Directive 2001/83/EC, as amended - complete and independent application, for product with known active substance and under the Optional Scope of Article 3(2)(b) – Therapeutic innovation of Regulation (EC) No 726/2004.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a liposomal prolonged-release dispersion for injection containing 13.3 mg/ml bupivacaine (expressed as bupivacaine base) as active substance.

Other ingredients are: dierucoylphosphatidyl choline (DEPC), dipalmitoylphosphatidylglycerol (DPPG), cholesterol, tricaprylin, sodium chloride, phosphoric acid and water for injections.

The product is available in 10 mL or 20 mL, single-use Type I glass vials with an ethylenetetrafluoroethylene-faced grey butyl rubber stopper, and an aluminium/polypropylene flip-tear-up seal.

Each vial of 10 mL prolonged-release dispersion for injection contains 133 mg bupivacaine.

Each vial of 20 mL prolonged-release dispersion for injection contains 266 mg bupivacaine.

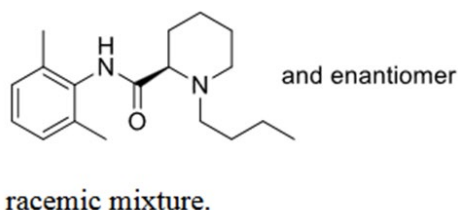
Note: During the procedure the name of the medicinal product changed (from 'Exparel' to 'Exparel liposomal') and the pharmaceutical form changed to a new EDQM standard term (from 'suspension for injection' to 'prolonged-release dispersion for injection'). The previous term "suspension for injection" was kept to express drug product pharmaceutical form throughout the MAA dossier Modules 1-5 and also may appear in this Assessment Report.

2.3.2. Active Substance

General information

The chemical name of bupivacaine is (*RS*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide corresponding to the molecular formula C₁₈H₂₈N₂O. It has a relative molecular mass 288.43 and has the following structure:

Figure 1: active substance structure



The active substance is a non-hygroscopic white or almost white crystalline powder, crystals or granules. It is soluble in methanol, ethanol and acetone and sparingly soluble in water and light petroleum ether.

Bupivacaine exhibits stereoisomerism due to the presence of one chiral centre and it is stated that it is manufactured as a racemic mixture.

Polymorphism has been observed for the active substance. Bupivacaine base can be observed in two polymorph forms (Form I and Form II). Both forms have been characterised. Bupivacaine base manufactured by the two active substance manufacturers corresponds to the stable polymorph Form I. Both forms can be distinguished by melting point. Bupivacaine HCl is the subject of a monograph in the Ph. Eur. but no Ph. Eur. monograph is available for the proposed bupivacaine base used as active substance in the finished product. There is indication that draft work has started on a monograph (02761) on EDQM's website.

Manufacture, characterisation and process controls

There are two manufacturers of active substance. The documentation on the active substance from both manufacturers is presented using an Active Substance Master File (ASMF) procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMFs and it was considered satisfactory.

Bupivacaine is synthesised using well defined starting materials with acceptable specifications. 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 carry-over of raw materials, impurities and solvents has been addressed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Discussion on impurities and on their mutagenic potential according to ICH M7 has been provided.

The active substance packaging materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC, GC, melting point), optical rotation (Ph. Eur.), colour of solution (UV), sulphated ash (USP / Ph. Eur.), loss on drying (USP / Ph. Eur.), water (USP / Ph. Eur.), related substances (HPLC, GC), 2,6-Xylidine (HPLC, GC), residual solvents (GC), assay (titration), microbial enumeration (USP / Ph. Eur.) and bacterial endotoxins (USP / Ph. Eur.).

Impurity limits were set in line with ICH Q3A guideline and Ph. Eur. requirements. Different residual solvents are controlled in the active substance from each supplier. Finished product manufacturer applies the same and/or equivalent analytical procedures as the manufacturers.

A suitable method for showing that the active substance is a racemate has been included in the specification of bupivacaine. Lack of test for polymorph form is acceptable considering that Bupivacaine is dissolved during the manufacturing process of finished product.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification and impurities testing has been presented.

Batch analyses data from the applicant for six recent batches of bupivacaine base active substance, three batches from each of the two suppliers has been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on twelve batches of active substance from one manufacturer stored in container representative of the commercial container-closure system for up to 48 months under long term conditions (25 °C / 60% RH) and on six batches for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines.

The following parameters were tested: appearance, identity, water, chromatographic purity, assay, 2,6-Xylidine, XRPD. All tested parameters were within the specifications. Photostability testing following the ICH guideline Q1B was performed showing the active substance is not sensitive to light.

Results on stress conditions (temperature (60°C), light (1.2 million lux hours given by ICHQ1b), moisture (>90% humidity), oxidative conditions using H₂O₂ and pH (pH 3, 5, 7, 9 and 11)) were also provided. There were no significant changes observed under the stress conditions apart from the degradation of Bupivacaine base found under oxidative conditions. As this degradant was not seen under accelerated conditions up to 21 months, it is not considered a degradant requiring control in the specification.

Stability data were provided on seven batches of active substance from the second manufacturer stored in container representative of the commercial container-closure system for up to 60 months under long term conditions (25 °C / 60% RH) and/or at 30 °C / 70% RH (to comply with ICH zone IVB conditions) and for up to 12 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines.

The following parameters were tested: appearance, colour of solution, water content, impurities by GC, 2,6-Xylidine, assay. All tested parameters were within the specifications. Photostability testing following the ICH guideline Q1B was performed showing the active substance is not sensitive to light.

Results on stress conditions (oxidative H₂O₂, temperature (105°C), light) were also provided. The forced degradation studies indicate that Bupivacaine is a rather stable compound. Degradation of Bupivacaine base was found under oxidative conditions, but not considered relevant to the commercial storage conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest periods of 48 months (first manufacturer) and 60 months (second manufacturer) in the proposed container with no special storage conditions.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Exparel liposomal prolonged release dispersion for injection is a sterile, white to off-white aqueous dispersion of multivesicular lipid-based particles (DepoFoam® drug delivery system) containing bupivacaine at a concentration of 13.3 mg/mL. The concentration of 13.3 mg/mL is expressed as bupivacaine base, which is equivalent to 15.0 mg/mL bupivacaine hydrochloride.

Exparel liposomal prolonged release dispersion for injection is provided in 133 mg/10 mL and 266 mg/20 mL vial configurations. It is packaged in Type I clear glass vials with ethylenetetrafluoroethylene (ETFE)-faced grey butyl rubber stoppers and aluminium/polypropylene flip-tear-up (FTU) seals.

There are also several process aids used in the manufacturing process but not present in the finished product.

The DepoFoam technology is based on a non-classical, multivesicular liposome (MVL) system. The MVL particles consist of a honeycomb-like structure with numerous non-concentric chambers containing drug dissolved in the internal aqueous phase. The aqueous chambers are separated from each other by lipid bilayers that are composed of phospholipids, cholesterol and triglycerides. A scanning electron micrograph of a DepoFoam particle is shown in Figure 2.

Figure 2: A scanning electron micrograph of a typical DepoFoam particle



Excipients

The full list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. DEPC (1,2-Dierucoyl-sn-Glycero-3-Phosphocholine) is a novel excipient in the finished product formulation. The other excipients are known pharmaceutical ingredients. Cholesterol, sodium chloride, phosphoric acid, water for injections and nitrogen are compendial excipients. It is considered that tricaprylin and DPPG (non-compendial excipients) are not-novel excipients since they have been previously registered in other medicinal products within the EU. Where relevant, the quality of excipients is compliant with Ph. Eur or other pharmacopoeial standards. Appropriate quality specifications have been set for the non-compendial excipients.

It is recommended that additional validation of the analytical methods used by the excipient manufacturer for control of microbiological purity for DPPG and tricaprylin and validation of method for control of bacterial endotoxins for tricaprylin should be submitted post approval. Furthermore, it is considered that the tests for unspecified impurities in DPPG and tricaprylin should be revalidated and the limit be tightened in line with Ph. Eur. The applicant agreed to these recommendations as a post approval commitment. (Note: Since the finished product manufacturer will test DPPG, tricaprylin batches for BET and microbial contamination, there are no concerns that non-compliant batches could be used in manufacturing process of finished product.

Novel excipient DEPC (1,2-Dierucoyl-sn-Glycero-3-Phosphocholine)

Two suppliers of the novel excipient DEPC are proposed. Full manufacturing process, quality controls and information on stability have been submitted in the quality dossier. A single consolidated DEPC specification including the tests, acceptance criteria and test methods for the two suppliers is provided by the finished product manufacturer.

All questions raised relating to the DEPC novel excipient from both suppliers have been resolved. It is recommended that additional confirmatory validation data of analytical methods for control of microbiological purity, bacterial endotoxins and impurity for DEPC should be submitted post approval. Furthermore, it is considered that the test for unspecified impurities in DEPC should be revalidated and the limit be tightened in line with Ph. Eur. The applicant agreed to these recommendations as a post approval commitment. (note: Since the finished product manufacturer will test DPPG, tricaprylin batches for BET and microbial contamination, there are no concerns that non-compliant batches could be used in manufacturing process of finished product.)

Formulation development

The development of the product including the selection of excipients is largely based on the prior knowledge on products (previously approved in Europe), that have been developed using multivesicular liposomes technology. The Quality Target Product Profile (QTPP) of the product was defined. The Critical Quality Attributes (CQA) were identified based on the QTPP. Formulations used in the various clinical trials were described.

Development of an *in vitro* release (IVR) test method has been described. During the procedure a major objection was raised regarding the proposed sampling points and acceptance limits for the IVR test. The applicant provided further data and additional explanation as well as statistical evaluation of approximately 3,000 commercial drug product batches manufactured since product approval in the US. CHMP concluded that it has been demonstrated that the proposed IVR test method provides reliable quality control of the product to assess manufacturing variability at initial release and to measure product stability, in combination with the other quality attribute tests in the finished product specification.

Manufacturing process development

Bupivacaine suspension for injection is manufactured via an aseptic process through a sequence of following steps: emulsification, solvent removal, buffer exchange, pooling, potency adjustment (as necessary), fill/closure.

Choice of sterilisation method was discussed in line with Decision Trees for Selection of Sterilisation Methods (Annex to NfG on Development Pharmaceuticals). The choice of aseptic processing is considered reasonable. During the procedure a major objection was raised on the theoretical risk of sterility/BET failure. In response, the applicant revised the specifications for active substance bupivacaine and for the excipients used for lipid solution preparation. The test parameters microbiological purity and bacterial endotoxin testing (BET) are now included in all the relevant active substance and excipient specifications.

Container closure system

The container closure systems consist of 10 mL and 20 mL Type I glass vials (13-mm neck), an ETFE (ethylenetetrafluoroethylene) faced grey butyl stopper, and an aluminum/polypropylene flip-tear-up (FTU) seal. The vial design studies were performed to identify the key parameters that affect the stability of the product during shipping. The target fill volumes have been set. Extractable studies performed on the vials and stoppers resulted in no extractables (vials) or very low levels of rubber oligomers (stoppers). According to results during stability study there was no differences in stability between vials stored upright and inverted indicating no adverse interaction between the product and stopper. In view of the extractable studies provided, migration studies are not necessary. The material complies 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.

Compatibility

The compatibility of bupivacaine suspension for injection with several implant materials (hernia mesh / PP and ePTFE, silicone materials, stainless steel and titanium alloys) were tested, the studies involved testing of exposed materials and key characteristics of finished product after exposure of product with implanted material for 7 days. It was concluded that characteristics of implanted materials are not affected by the exposure to finished product.

Exparel suspension for injection could be administered undiluted or diluted. Study regarding compatibility of bupivacaine suspension for injection and 0.9% NaCl solution and Ringer's lactate has been done by the applicant. Different dilution factors were used for a.m. solutions. The content of free bupivacaine was chosen as indicator of compatibility. Conclusion is that increase of free bupivacaine is directly proportional to the dilution factor used (if dilution factor is higher, increase of free bupivacaine is observed).

Effect of storage time in syringe after dilution with 0.9% NaCl solution has been studied. Dilution factors 1, 2, 15 were used. There were additional slow increases in free bupivacaine after dilution with 0.9% NaCl solution and when stored at 25°C. No effect on particle size distribution and pH has been observed.

It has been confirmed that needle size and mixing order has no influence on the quality of Exparel and it should be administered with a 25 gauge or larger bore needle.

Compatibility of Exparel with some local anaesthetics has been provided. Conclusion is that Bupivacaine hydrochloride and Exparel may be administered simultaneously in the same syringe, and bupivacaine hydrochloride may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine hydrochloride solution to Exparel does not exceed 1:2. Non-bupivacaine based local anaesthetics, including lidocaine, may cause an immediate release of bupivacaine from Exparel if administered together locally. The administration of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more.

According to studies Exparel could be compatible with epinephrine, bacitracin, cefazolin, gentamycin, morphine sulfate, ketorolac tromethamine. It could be co-administrated with cefuroxime, clonidine, tranexamic acid. The applicant stated that a.m studies were performed in order to better understand medicinal product characteristics and no addition to product information is proposed at this stage.

Exparel is not compatible with dosing combinations containing local anaesthetics such as Naropin (ropivacaine) and should not be mixed prior to administration with corticosteroids.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: emulsification solvent removal, buffer exchange, pooling, potency adjustment (as necessary) and fill/finish (depyrogenated glass vials, sterilised stoppers and aluminium caps). The process is considered to be a non-standard manufacturing process.

Sterilisation cycles/conditions of primary packaging components are described. Vials are dry-heat sterilised using a depyrogenation tunnel. A temperature greater than 220°C for a validated time is used with demonstration of a 3-log reduction in heat resistant endotoxins. Stoppers are steam sterilised using autoclave following Ph. Eur. reference Cycle ($\geq 121^\circ\text{C}$ for ≥ 15 minutes). Full characterisation of used filters is provided. Furthermore, the applicant has confirmed that all solution filters are for single use only.

In-process control parameters and limits are described and are adequate for this type of manufacturing process / pharmaceutical form.

Proposed holding times based on process validation results as well as aseptic process simulations are confirmed. The applicant has clarified that proposed time is required to complete entire manufacturing process and carry out all quality control tests. Risk Assessment to evaluate potential risks to product sterility and other product quality attributes was initiated by the applicant and found the risk to be low. Sterility assurance of the holding process and maximum holding time is verified in semi-annual media runs.

The applicant has confirmed that the expiration period of a batch is calculated in accordance with the EU guideline NfG on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/ 072/96).

Process validation was performed. Media fill data summary are provided to support aseptic process and holding times. Suitability of sterilising filters used in the manufacture of finished product has been demonstrated. Filled, stoppered and sealed vials were challenged for container-closure integrity (by dye ingress testing followed by microbial challenge testing) and found to be integral. It has been

demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner

Product specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance, identity (UV, HPLC), total bupivacaine (HPLC), free bupivacaine (centrifugation/HPLC), packed particle volume (PPV) (centrifugation), bupivacaine degradation products (HPLC), cholesterol (HPLC), particle size distribution (laser light scattering), *in vitro* release (HPLC), pH (glass electrode), residual solvent (GC), lipid degradation (HPLC), particulate contamination: subvisible particles (Ph. Eur.), osmolality (vapour pressure osmometry), uniformity of dosage units (Ph. Eur.), extractable volume (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The finished product is released on the market based on the release specifications, through traditional final product release testing. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Proposed specification follows general recommendations provided in ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances; ICH Q3B (R2) Impurities in new drug products (CPMP/ICH/2738/99) (reporting threshold 0.1%, ID threshold 0.2%, qualification threshold 0.2%) and European Pharmacopoeia. The total bupivacaine content is specified as 95.0% – 105.0% of the declared content at release and shelf-life. The acceptance criteria of all specification parameters are considered justified, they are based on the batch release and stability data or are compliant with the Ph.Eur. requirements or quality guidelines.

Potential impurities in the finished product originate from the active substance (bupivacaine free base), the lipid components (DEPC, DPPG, tricaprylin, and cholesterol), and the processing aids used in the finished product manufacturing process. Hydrolysis of the amide bond in bupivacaine produces Ph. Eur. impurity F (2,6-xylidine) and N-butyl-2-piperidine carboxylic acid, in equimolar ratio, therefore only Ph. Eur. impurity F is controlled in the finished product specification. An oxidation product of bupivacaine is controlled in the finished product specification.

These potential impurities in the finished product are sufficiently described and proposed limits for specified and unspecified impurities are acceptable including limit for 2,6-Xylidine which does not exceed the level of acceptable daily intake of mutagenic compounds recommended in ICH M7 based on less conservative approach of LTL exposure. The acceptance criteria for individual and total impurities comply with the batch results, stability studies taking into consideration the natural variance of results or are even tighter than Q3B(R2) requirement therefore is acceptable. During the procedure a major objection was raised on the applicant's initial proposal to exclude impurities testing from shelf-life specification. In response the applicant updated the shelf-life specification to include the parameter for control of degradation products, which was considered acceptable. Additional potential bupivacaine related impurities deriving from the active substance synthesis which are not bupivacaine degradation products are controlled in the active substance.

During the procedure a major objection was raised regarding the exclusion of lipid degradation products from the finished product specification. Extensive justification of potential lipid degradation products in finished product and control strategy was submitted and supported by forced degradation studies. Impurities derived from synthesis of the lipids are controlled in each individual lipid component. Discussion of impurities with mutagenic potential as per requirements of ICH M7 was submitted. In summary, Leadscope expert rule-based and statistical assessment is performed, 4 impurities are

classified as Class 3 impurities and are controlled below TTC, the rest of impurities are classified as Class 5.

The applicant reviewed the product for potential presence of nitrosamine impurities and conducted a risk evaluation. All potential route sources of nitrosamines impurities are considered in the risk assessment. Despite the fact that three raw materials and a number of impurities and degradation products have the potential to be nitrosable substances, no nitrosating agents are used and are not present as impurities in the Exparel manufacturing process, therefore, the risk of nitrosamines formation in the Exparel manufacturing process is negligible.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities, Option 2B. Batch analysis data on 3 batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Batch details and batch analyses data are provided for more than 100 batches of finished product used in clinical studies, toxicology studies, stability studies to register the product in the US, process validation, and recent commercial lots manufactured for U.S. distribution. The analytical methods used for initial release testing of the U.S. FDA registration batches, process validation batches and recent commercial batches presented in the batch analyses tables are the same as those described the current dossier. The batch data complies with the proposed specification and are consistent between batches and manufacturing sites.

Stability of the product

Stability data from 60 batches of finished product stored for up to 30 months under long term conditions ($5^{\circ}\text{C}\pm 3^{\circ}\text{C}$) and for up to 6 months under accelerated conditions ($25^{\circ}\text{C} / 60\% \text{RH}$) according to the ICH guidelines were provided. The batches of Exparel are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The studies included batches manufactured at both sites. Different suppliers of excipients (DEPC, cholesterol) and active substance were used for manufacturing of medicinal product batches used in stability studies.

Batches were tested for parameters susceptible to change during storage: appearance, total bupivacaine, free bupivacaine, packed particle volume, bupivacaine degradation products, particle size, *in vitro* release, pH, lipid degradation, particulate contamination, bacterial endotoxins and sterility.

At long term storage conditions the obtained results for all parameters are according to specification. At accelerated conditions appearance of the suspension changed (aggregation) and particle size also increased. Some additional studies have been performed by the applicant investigating the effect of temperature cycling, photostability, freezing, effect of mechanical stress and storage configuration, in-use stability in PP syringes, acid and base hydrolysis and oxidative degradation have been studied. It was confirmed that finished product is not sensitive to temperature cycling between 5°C and 25°C , hydrolytic degradation and to light exposure, but is sensitive to temperatures above 40°C and to oxidation as well as to freezing. Minimal sensitivity to mechanical stress is confirmed. Sensitivity to elevated temperatures resulting in possible aggregation after certain period of time accompanied by increase in particle size, free bupivacaine content and lipid degradation is also confirmed.

To demonstrate the effect of mechanical stress on the quality of Exparel, the applicant has provided shipping study data, which additionally justify the increased limit of free bupivacaine in shelf life specification.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on these results, the drug product packaged in clear Type I glass vials is stable upon exposure to light and does not require further protection.

The proposed in-use shelf-life of 48 h at 5°C and 6 h at 25°C of the medicinal product in PP syringes is acceptable and supported by the submitted data. After dilution, chemical and physical in-use stability of Exparel when admixed with other formulations of bupivacaine has been demonstrated for 24 hours at room temperature (below 25°C). When admixed with 9 mg/mL (0.9%) sodium chloride or lactated Ringer's solution, chemical and physical in-use stability has been demonstrated for 4 hours when stored in a refrigerator (2°C to 8°C) and at room temperature (below 25°C).

Based on available stability data, the proposed shelf-life of 2 years with storage conditions 'store in a refrigerator (2-8°C), do not freeze' as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

Except for cholesterol all other excipients are from non-animal and non-human origin.

A TSE/BSE statement is provided from each ASMF holder/active substance manufacturer to confirm that the active substance Bupivacaine base is manufactured without any material of animal or human origin. Adequate TSE/BSE statements from the manufacturers of three non-compendial excipients (DEPC, DPPG and tricaprylin) are also provided. For cholesterol, the only excipient of animal origin, current valid versions of TSE CEPs are enclosed.

Other compendial materials (phosphoric acid and sodium chloride) used in the manufacture of bupivacaine, suspension for injection are chemicals that should not be a source of adventitious agents.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

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

The major objections raised during the procedure have been satisfactorily resolved.

MO on sterility assurance was resolved as the applicant added the test parameters microbiological purity and bacterial endotoxin testing (BET) in all relevant active substance and excipient specifications.

MO on applicant's initial proposal to exclude impurities testing from shelf-life specification was resolved as the applicant updated the shelf-life specification to include a parameter for control of degradation products.

MO regarding the proposed sampling points and acceptance limits for the IVR test was resolved as applicant provided further data and additional explanation as well as statistical evaluation of approximately 3,000 commercial drug product batches manufactured since product approval in the US.

MO regarding the exclusion of lipid degradation products from the finished product specification was resolved by adding a test for lipid degradation to finished product specification, supported by extensive justification of potential lipid degradation products in finished product, the control strategy and forced degradation studies.

The applicant reviewed the product for potential presence of nitrosamine impurities and conducted a risk evaluation. The risk of nitrosamines formation in the Exparel manufacturing process is negligible.

At the time of the CHMP opinion, there were a number of minor quality issues having no impact on the Benefit/Risk ratio of the product. These are addressed below as recommendations for future quality development.

2.3.5. 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.

2.3.6. 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:

1. Validation of the analytical methods used by the excipient manufacturer for control of microbiological purity for DEPC, DPPG and tricapyrylin and validation of methods for control of bacterial endotoxins for DEPC and tricapyrylin should be performed and submitted.
2. Additional validation of the analytical method used by the excipient manufacturer for control of peroxide value of DEPC should be performed and submitted.
3. The excipient manufacturer should evaluate the DEPC method for control of impurities and, if a new method is needed, its development and validation should be completed. Should the evaluation conclude that the current method is suitable but needs additional validation, this too should be completed. Once a suitable method is validated with the tightened limit for unspecified impurities the respective sections should be updated accordingly, and the change reported by means of an appropriate variation procedure.
4. The excipient manufacturer should evaluate the DPPG method for control of impurities and, if a new method is needed, its development and validation should be completed. Should the evaluation conclude that the current method is suitable but needs additional validation, this too will be completed. Once a suitable method is validated with the tightened limit for unspecified impurities included in the specification, the respective sections should be updated accordingly, and the change reported by means of an appropriate variation procedure.
5. The excipient manufacturer should evaluate the Tricaprylin method for control of impurities and, if a new method is needed, its development and validation should be completed. Should the evaluation conclude that the current method is suitable but needs additional validation, this too will be completed. Once a suitable method is validated with the tightened limit for unspecified impurities the respective sections should be updated accordingly, and the change reported by means of an appropriate variation procedure.

Note: The excipient manufacturer has committed to address these quality recommendations.

2.4. Non-clinical aspects

2.4.1. Introduction

The nonclinical program was designed to support the administration of Exparel as a field block and as a peripheral nerve block; however, other routes have been tested and the results are presented to further support the safety of Exparel. The toxicology program also included additional studies on placebo (DepoFoam containing no bupivacaine) in order to qualify the excipients, including dierucoyl

phosphatidylcholine (DEPC) and tricaprylin. DEPC is a novel excipient in Exparel and has not been used in the formulation of any previously approved pharmaceutical products in the European Union (EU). In addition, references were provided to published literature to support other aspects of the nonclinical programme.

2.4.2. Pharmacology

Primary pharmacodynamic studies

Exparel was developed to provide prolonged local or regional analgesia via a single administration as a field block or peripheral nerve block.

The mechanism of action and the pharmacological profile of the local anaesthetic bupivacaine, the local and regional anaesthetic properties and the analgesic effects of bupivacaine have been extensively characterised and described in the literature. Adequate literature review has been submitted. In-depth pharmacological investigations on bupivacaine alone or in combination with other drugs have not been conducted because the effects of bupivacaine have been well documented in various efficacy models in the rodent and other species.

Given the decades of clinical experience with IR bupivacaine in the proposed indications and the well characterised pharmacological action of bupivacaine in the literature, the primary pharmacodynamic evaluation was limited to one study in guinea pigs using a dermal wheal/pin prick model to evaluate the duration of anaesthetic effect and injection site irritation. Non-GLP pilot study RES 0801 SKY0402-059 suggests that Exparel produces a sustained analgesic effect compared with IR bupivacaine in a dermal wheal/pin prick model in guinea pigs. The objective was to study the duration of anaesthetic effect and injection site irritation of DepoBupivacaine and bench-scale placebo administered by intradermal injection in a guinea pig wheal/pin prick model. DepoBupivacaine was found to have good antinociceptive activity through at least 6 hours compared to IR Bupivacaine. At the highest dose (17.72 mg/mL) it caused a well-defined erythema.

The data obtained from this study are not considered of sufficient quality to generate definitive conclusions regarding the effectiveness of Exparel; however, given that the mechanism of action of bupivacaine that is released from DepoFoam is indistinguishable from commercially available bupivacaine HCl solutions, and the fact that bupivacaine (as bupivacaine HCl) has been marketed worldwide for over 50 years and thoroughly studied, it can be considered that the provided data altogether provide sufficient evidence to prove the effects and mode of action of Exparel. In addition, the data from performed GLP toxicology studies support the efficacy and mode of action of Exparel.

Secondary pharmacodynamics

Secondary pharmacodynamics profile of bupivacaine has been described in the literature. Published results have demonstrated that bupivacaine interacts with various components of the immune system, and may reduce inflammatory pain, inhibit bacterial growth, possibly even mitigate perioperative inflammatory injury and protect against epidural abscesses. Secondary PD evaluation was limited to a one non-GLP *in vitro* study: In Vitro Effect of SKY0402 on Whole Blood Coagulation Using Activated Clotting Time. The objective was to evaluate whether SKY0402 in clinically relevant concentrations interferes with whole blood coagulation, as measured by activated clotting time (ACT) using a Hemochron instrument. The *in vitro* data were compared to results obtained with bupivacaine HCl solution. The results of non-GLP study CeeTox 9032-081 demonstrate that both Exparel and IR bupivacaine at high concentration (8.86 µM) slightly prolonged ACT in human blood at 1 hour of exposure. There was no detectable difference in ACT between Exparel (1.4 or 2.9 µg/mL) and saline control at 3 hours. The

concentrations of SKY0402 and bupivacaine HCl solution used in this experiment are considered clinically relevant.

Safety pharmacology

As the safety pharmacology of bupivacaine is well characterised, no formal studies on liposomal bupivacaine have been conducted and a review of relevant published literature references was provided.

The effects of bupivacaine acting on the neurological and cardiovascular systems have been well documented in the medicinal literature. Because the same types of Na⁺ channels are present in most types of neurons, bupivacaine blocks impulse conduction in all types of nerve cells, including sensory, motor, autonomic, and CNS neurons. Bupivacaine affects electrocardiography parameters. In increasing concentrations, it can produce bradycardia, diminished contractility, atrioventricular blockade, vasodilation, and eventually cardiac arrest. Animal studies of bupivacaine have shown that bupivacaine increases both QRS and QTc duration, and decreases CO. These results have been shown in multiple models, including dogs, rabbits, and piglets. However, the concentrations seen are greater than the ones seen in human studies. Changes to PK, electrocardiogram (ECG), blood pressure, and respiration parameters were also evaluated as part of the nonclinical toxicology programme for Exparel.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies of Exparel have not been performed. A review of relevant published literature references was provided. Drug interactions of bupivacaine are well defined through existing literature and the long-standing experience of the therapeutic use of bupivacaine. Exparel is expected to have a similar drug interaction potential as bupivacaine. Although the DepoFoam component of Exparel has no known pharmacodynamic drug interactions, Exparel should not be mixed with local anaesthetics other than IR bupivacaine due to their potential to displace and release bupivacaine from DepoFoam.

2.4.3. Pharmacokinetics

Given the long history of clinical use of bupivacaine, an abridged nonclinical program was designed and executed to support the clinical development. Additional distribution, metabolism, and excretion studies were not conducted. This is considered acceptable as the distribution, metabolism, and excretion of bupivacaine after release from the DepoFoam particles *in vivo* are expected to be the same as IR bupivacaine.

Absorption

The absorption properties of bupivacaine are well documented in the literature. As a part of the Exparel development program, the applicant conducted PK studies to determine the rate of bupivacaine release from DepoFoam and systemic exposure over time.

The retention of bupivacaine at the injection site following intradermal or subcutaneous (SC) administration of Exparel or Placebo (DepoFoam containing no bupivacaine) was studied in rats and guinea pigs. The PK of the retention of Exparel components in addition to DEPC (ie, DPPG, tricapyrylin, cholesterol) at the site of injection was studied in rats. Of the three lipids at the site (DEPC, tricapyrylin, and cholesterol), tricapyrylin disappeared more quickly than DEPC and cholesterol.

In addition, the absorption and PK of Exparel was compared with that of IR bupivacaine. PK analyses of pilot and development scale Exparel test/control materials is provided, which includes batches used in PK studies, toxicology studies, and clinical studies. PK data for clinical lots following SC administration in the rat model are also presented. In addition, process variants and effect of storage and temperature was studied following SC administration in the rat.

Distribution

The distribution of bupivacaine has been extensively characterised in the scientific literature and there is long standing experience on the therapeutic use with approved bupivacaine medicinal products in Europe. The only distribution study that was conducted using Exparel was Study 16-SS-085, which was designed to determine whether bupivacaine-containing Exparel liposomal particles are sequestered within the blood cell fraction (whole blood, RBC pellets, and plasma) from beagle dogs following centrifugation. The results of Study 16-SS-085 suggest that there was no difference in the distribution of bupivacaine between the dogs treated with IR bupivacaine vs. Exparel.

Metabolism

No formal metabolism studies of Exparel were conducted. The metabolism of bupivacaine is well characterised, and a set of comprehensive reviews and published literature references have been provided.

Excretion

No formal excretion studies of Exparel were conducted. The excretion of bupivacaine is well characterised, and relevant literature information has been provided.

Pharmacokinetic drug interactions

Drug interaction studies were focused on co-medications that may be administered to patients in the surgical setting prior to Exparel injection as part of multimodal analgesia (e.g., lidocaine/epinephrine or IR bupivacaine, frequently used as adjuncts to general anaesthesia). The mini-pig model is considered adequate to investigate the potential interaction of Exparel with lidocaine or IR bupivacaine because of its similarity (regarding the morphology and physiology) to humans.

The PK profile for the different groups appeared to be a cumulative profile of Exparel and IR bupivacaine. The extended-release profile of Exparel was not compromised. Apparent half-life ($t_{1/2}$) and t_{max} for

bupivacaine were not altered by the administration of IR bupivacaine concomitant with or prior to Exparel (S08668). Consistent with its extended-release properties, Exparel has a relatively modest effect on plasma concentrations when used in combination with IR bupivacaine solution (pre-mixed) or from sequential administration of IR bupivacaine followed by Exparel at doses up to 4 times that of IR bupivacaine and a wait time of up to 15 minutes.

Based on the PK drug interaction studies (S07580 and S07607), administration of Exparel with lidocaine within 5 or 10 minutes to mini-pigs produced maximal interactive effects on systemic exposure parameters (C_{max} and AUC). The susceptibility of Exparel to interact with lidocaine could be reduced by a 20- or 40-minute time interval after administration of lidocaine mixture, prior to Exparel administration (S07607).

Distribution of Dierucoyl phosphatidylcholine (DEPC)

The study QPS-137N-0401 objective was to determine the tissue distribution of DEPC and DEPC related material following a single, subcutaneous (SC) administration of a DepoFoam formulation containing [14C-labelled DEPC] to male, pigmented rats using quantitative whole-body autoradiography (QWBA). There are no data provided regarding metabolites of DEPC. DEPC is a synthetic homolog of dioleoylphosphatidylcholine (DOPC) which is a natural lipid. Lipids such as DOPC and DEPC are subjected to oxidation of the fatty acid to generate energy or synthesise new lipids for storage. Once the DepoFoam vesicle is broken down into individual components DEPC is expected to follow the lipid catabolism pathways similar to a natural fatty acid.

Distribution of Exparel lipid components in addition to DEPC (ie, DPPG, tricaprylin) was not evaluated. The applicant stated that regarding absorption, distribution, metabolism, and excretion of the phospholipid (DOPC, DEPC, and DPPG) and neutral lipid (cholesterol, triolein, tricaprylin) components of the DepoFoam matrix, since these are all naturally occurring or synthetic analogues of common lipids, the metabolic fate of these excipients is expected to be similar to that of endogenous lipids. The applicant presented an overview of expected absorption, metabolism and excretion of lipid components of DepoFoam.

In summary, the pharmacokinetic results confirm the performance characteristics of the DepoFoam delivery system in all species tested.

2.4.4. Toxicology

Given the long history of clinical use of bupivacaine, an abridged toxicological program was designed and executed to support the clinical development and the MAA of Exparel. This included single and repeat dose toxicity studies to evaluate the potential local and systemic toxicity of Exparel relative to IR bupivacaine, placebo, and/or saline. Given the long history of therapeutic use of bupivacaine, and the proposed single dose use of Exparel, no genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies of Exparel were conducted. Relevant information is provided from a review of the literature.

The toxicology program included studies on Placebo (DepoFoam containing no bupivacaine) in order to qualify the excipients.

Single dose toxicity

Single dose toxicity studies with Exparel were performed in rats, dogs and rabbits utilizing same route of administration as it is intended in clinic (subcutaneous infiltration and perineural field block). In dogs and rabbits a surgical model was performed to assess acute toxicity and effect on wound healing as compared with bupivacaine HCl or saline.

The applicant performed 3 studies with Placebo using IV route and 3 studies IV and IA route of administration as a way to qualify toxicity of the product and liposomal particles if it is to be accidentally administered IV or IA in clinical practice. Animals used were rats and dogs. In addition, 2 studies were performed using epidural and intrathecal route of administration.

Histopathological findings from the SC toxicity of Exparel in rats (20995, GLP) indicated statistically significant higher rates of chronic inflammation in subcutis and muscle tissue in female subjects when compared to males (data compared with Saline group at Day 3 post-injection).

Repeat dose toxicity

Repeat dose toxicity studies were performed with Exparel and Placebo. Pivotal toxicity studies with Exparel were performed in rabbits (4 weeks with twice weekly dosing and 4 weeks recovery) and dogs (4 weeks with twice-weekly dosing and 4 weeks recovery; 26 week monthly injections as femoral nerve block with 12 week recovery period). Due to the history of clinical use of bupivacaine, repeat dose toxicity studies of Exparel were not conducted in rodents.

Repeat dose toxicity studies with placebo were performed in rats (28 consecutive days SC with 14 days recovery period) and dogs (28 consecutive days with 28 days recovery period).

There was no evidence of neural degeneration after nerve block in rabbits or dogs, or degeneration of spinal cord tissues after ED dosing in rats or dogs.

Convulsions were seen in NZW rabbits (MPI-947-036) with Exparel at 7.97 and 15.95 mg/kg, similar to IR bupivacaine at 7.97 mg/kg. The convulsions appeared to be associated with bupivacaine, and not the liposome formulation; however, it is unclear why convulsions were not seen at the highest bupivacaine level of 26.58 mg/kg. The absence of systemic effects with the highest dose of Exparel is likely due to biological variability and could have been further explored. Nevertheless, the same administration scheme in the beagle dogs (study MPI-947-037) caused no such effects at either dose supporting safety of the Exparel.

Exparel-related effects observed in the beagle dogs (MPI-947-037) were associated with the injection sites. With the low incidence and severity observed in these animals, this effect was considered to be an expected response to the liposomes and non-adverse. The high dose level of 26.58 mg/kg/dose was considered to be the NOAEL.

The only Exparel-related microscopic finding was minimal focal granulomatous inflammation in the fascia of the skeletal muscle surrounding the injection site at the 24 mg/kg dose group, which completely recovered during the 12-week recovery period. Due to the absence of Exparel-related changes at the mid dose level, 16 mg/kg was considered the No-Observed-Effect Level (NOEL). Based on the evidence of complete reversal for the microscopic findings at 24 mg/kg, this dose was considered the NOAEL.

Genotoxicity

No formal *in vitro* and *in vivo* genotoxicity/mutagenicity studies were performed as part of the nonclinical program to assess the mutagenic and clastogenic potential of Exparel. The applicant refers to published literature. In addition, Placebo did not show any evidence of genotoxic activity in *in vitro* and *in vivo* tests.

Carcinogenicity

No formal carcinogenicity studies on Exparel were performed as part of the nonclinical program. In accordance with ICH Topic S1A *The Need for Carcinogenicity Studies of Pharmaceuticals* for

pharmaceuticals administered infrequently or for short duration of exposure (e.g., anaesthetics and radiolabeled imaging agents) do not need carcinogenicity studies unless there is cause for concern. No cause of concern was raised from the results of repeat dose toxicity studies conducted with Exparel.

Reproductive and developmental toxicity

No studies on reproductive and developmental toxicity were conducted with Exparel. A comprehensive review on available information for bupivacaine is provided.

Reproductive toxicology of the Exparel Placebo (DepoFoam containing no bupivacaine) was evaluated in studies on embryofoetal development in rats and rabbits, and in a combined fertility and peri/postnatal study in rats.

Epidural and Intrathecal Administration of Exparel

Other routes of administration of Exparel, such as single dose epidural, and potential inadvertent intrathecal administration, were also explored in GLP compliant studies in rats (MPI 947 031) and dogs (MPI 947 020) using IR bupivacaine for comparison. The performed studies were designed, performed and evaluated in line with the current regulations and recommendations.

Local tolerance

The applicant assessed local tolerance as part of the repeat dose toxicity studies, some of the single dose toxicity studies and performed separate studies of local tolerance including evaluation of injection site gross pathology and histopathology. Stand-alone studies of local tolerance were performed in guinea pigs, rabbits and dogs.

Studies on the excipients

An extensive toxicology program for Placebo (DepoFoam MVL) was performed. In order to provide the osmotic balance for Placebo, sucrose, lysine monohydrate, and phosphoric acid were used to adjust osmolality inside the multivesicular liposomes.

Studies on the excipients (including DEPC and tricaprylin) have indicated that they are without significant local or systemic toxicity at single or repeated doses, and that it has no genotoxic, teratogenic, or developmental effects. The repeat-dose toxicity studies with Placebo revealed no significant local or systemic adverse effects in rats and dogs. In each species, the local injection reactions showed progress towards resolution after 14- or 28-Day recovery periods, respectively.

Studies on impurities

Studies on qualification of impurities are not needed to support this MAA as the impurities do not exceed ICH recommended levels.

2.4.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment was performed to evaluate potential environmental risks of Exparel containing the active moiety bupivacaine. The submitted ERA relies on Phase I assessment.

Estimation of exposure in phase I was based only on drug substance, which is considered acceptable. Indication covered in assessment was prolonged acute pain management and reduction in need for opioids in adults compared to immediate release bupivacaine, with maximum daily dose of 266 mg of bupivacaine (20 ml of Exparel, concentration 13,3 mg/ml). Bupivacaine is a known substance widely used

in existing authorised products in the EU. The measured partition coefficient values of bupivacaine are below 4.5 (i.e., 0.5 at pH 5, 2.2 at pH 7 and 3.1 at pH 9). Therefore, it is not identified as a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance. As bupivacaine metabolites are expected to be more soluble in water than the parent drug substance, the risk for bioaccumulation of metabolites is also considered to be acceptable.

Two calculations of the Phase I PEC_{SURFACEWATER} of bupivacaine (0.0036 and 0.0027 µg/L) did not exceed the action limit of 0.01 µg/L. Based on pre-clinical data of toxicity in developmental and reproductive toxicity studies in mammalian species, bupivacaine is not expected to affect the reproduction of vertebrate or lower animals at concentrations lower than the action limit of 0.01 µg/L. Therefore, a further Phase II environmental fate and effects assessment is not required.

Table 1

Substance (INN/Invented Name): bupivacaine			
CAS-number (if available):			
PBT screening		Result	Conclusion
PBT-assessment			
log D _{ow}	EC A8	0.5 at pH5	Potential PBT (N)
	OECD107	2.2 at pH7	
logP _{ow}	OPPTS	3.1 at pH9	
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	0.0036 and 0.0027	µg/L	> 0.01 threshold (N)

Bupivacaine PEC_{surfacewater} value is below the action limit of 0.01 µg/L and is not a PBT substance as log D_{ow} (log P_{ow}) does not exceed 4.5.

2.4.6. Discussion on non-clinical aspects

Given the long history of clinical use of bupivacaine, an abridged nonclinical program was designed and executed to support the clinical development. In addition, references are provided to published literature to support other aspects of the nonclinical programme.

Studies were designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific, contemporary scientific standards, and in consideration of applicable regulatory requirements. No major deviations were made from the GLP study protocols.

Primary pharmacology

Pharmacology of this drug product is based on an assumption that DepoFoam is responsible for its innovative mode of action. The precise mechanism involved in release of bupivacaine from DepoFoam

particles is unknown. Two mechanisms were proposed: 1) Reorganisation of lipid membrane due to tricaprilyn becoming a liquid oil at body temperature and leaving particles for partition into the surrounding tissues leading to particle destabilisation. Unstable particles break down and release bupivacaine, 2) Diffusion of free base bupivacaine from the particles. In the particles, there is a small fraction (0.001) of bupivacaine present in the free base form which is uncharged, allowing it to cross membranes. Released bupivacaine will drive further diffusion of bupivacaine base out of the liposomes to maintain equilibrium.

Exparel is a specific innovative product with bupivacaine as a known active substance for which the pharmacology of the active substance is well known from extensive clinical practice and clinical literature from a period of over 50 years. There is no need to demonstrate primary pharmacodynamics in theory. Proof of concept for this product is in fact the proof of adequate pharmacokinetic profile in which the applicant has to prove prolonged release of bupivacaine on the site of application in the desired amount. Thus, the non-clinical study of primary pharmacodynamics of this drug product design could be completely omitted in theory and focus placed on clinical PD of proposed formulation.

Nevertheless, some points need to be noted. The applicant submitted one study in which pharmacodynamics of the Depo bupivacaine formulation is demonstrated. Although the wheel/pin prick model is a known testing model in animals for local anaesthetic, it may not be appropriate for the proposed drug formulation because it is important for DepoBupivacaine to prove that it remains at the injection site after SC injection or routes other than i/d. In this study the drug is applied intradermal, which is not same as future clinical use. According to the applicant, longer retention has been demonstrated compared with IR bupivacaine, but the method used is questionable, since kinetics are different when applied intradermal and subcutaneous. There is a claim in the study that a series of sub-studies was conducted which were performed in guinea pigs and rats to establish the animal model and feasibility of analytical method and that DepoBupivacaine was well tolerated in both Guinea pigs and rats following subcutaneous dosing, but DOC#91325 to which the applicant refers to is not presented. Results presented scarcely support prolonged analgesia claim since it is visible that after 48 hours only 2 out of 5 pricks in the inner circle are negative with the highest dose applied (20 mg/mL). In the lower dose groups, there was no effect of Depo bupivacaine after 18 h. Also, there is no explanation why the animals were observed for 48 hours since the prolonged analgesia is claimed to be up to 72 hours in clinical setting. Several other problems were identified in the submitted study. 1 ml was used intradermal which seems as a large volume for this route of administration and is a quite larger volume from those advised in literature (0,1 ml, *Vogel, 2002.*). It seems that only DepoBupivacaine was used per one animal. There was no control (standard) used in a second wheal on the same animal. The study from which the results of tests with IR are derived are not presented for verification of claims (RES-0301-SKY0402-018). Results of rat studies and SC guinea pig studies are not presented. Several errors in the report were noted, among others the species "Sprague Dawley male guinea pigs, Harlan", seems it is not one species. Figures presented are not visible adequately. These are not considered very important concerns since it is a pilot study report for a well-established substance but it has to be noted.

Secondary pharmacodynamics

Inhibition of coagulation by local anaesthetics *in vitro* is an effect already recorded in published literature (*Ti and Li, 1999., Tobias et al., 1999., Kohrs, 1999.*) and is not considered a major safety risk which could lead to prolonged bleeding in clinical setting at present time point. The applicant conducted an *in vitro* study on whole blood coagulation using activated clotting time but the last time point was 3 h post application of bupivacaine. Both bupivacaine HCl solution and SKY0402 at high concentration (10 µM) slightly prolonged ACT in human blood at the 1-hour exposure and no effects were seen at 3 hours in this *in vitro* study. In the single-dose epidural and intrathecal toxicity study in dogs, there was a slight prolongation of the APTT in animals receiving IR bupivacaine or Exparel/Xylocaine. Although mild, this was considered treatment-related. The applicant argues that no effect on PT and APTT is seen in the

repeat-dose subcutaneous toxicity studies. In Exparel repeat-dose toxicity studies in dogs (947-037) and rabbits (947-036), APTT and PT were investigated pre-test and prior to terminal and recovery necropsies. There were no test article-related effects on these parameters.

Lack of dedicated safety pharmacology studies and non-clinical PD studies is acceptable as a summary of the assessments from toxicology studies conducted with bupivacaine/Exparel and the published literature on bupivacaine are provided.

Pharmacokinetics

Absorption

Study RES-0702-D0402-044 indicates that sustained release of bupivacaine occurs with DepoBupivacaine formulations as compared with a simple aqueous solution of bupivacaine. For both glucuronate and phosphate lots, plasma bupivacaine levels were observed throughout 72 hours. Phosphate lot showed somewhat lower C_{max} with a slower release of bupivacaine compared to glucuronate lot.

The applicant presented a study report (RES-73965), which is a compilation of several experimental studies conducted in early stages of development of drug product, which makes it difficult to follow.

The applicant states that DEPC enters normal metabolic pathways upon absorption and, although a similar study has not been performed with the other lipid components, it may reasonably be expected that they undergo the same fate. DEPC remains on the site of administration longer than bupivacaine i.e. bupivacaine disappeared more rapidly than DEPC. The applicant concludes that DEPC disappeared more rapidly from the tissues between 7 and 14 days, and has disappeared completely from the site by 21 days. This can only be stated for the guinea pig i/d part of the study which was followed up till day 21. Other studies are not followed up after day 7 or 14.

In the study RES-73965 there are differences between remaining dose of DEPC on day 7 in rats when given subcutaneously with and without bupivacaine (58% of injected dose remains on sight on 7th day when given with bupivacaine and 25.8% of injected dose remains when given as placebo, both administered initially with the same amount of DEPC). It seems that the DEPC particles remain longer and are more persistent in the guinea pig (93% of injected dose of DEPC on day 7 in both SC and intradermal administration) regardless of the remaining bupivacaine content on the site on day 7 (4.3% when administered i/d, 23 %when administered SC). In other animals and other routes of administration, there is no follow up after 7 or 14 days. Regarding differences in the remaining dose of DEPC on day 7 in rats, the applicant argues that the rate of decline in amount of DEPC is comparable because difference in remaining dose of DEPC is due to the variation in measured starting concentrations between groups (Exparel 119%, Placebo 97%). The applicant concludes that DEPC disappeared more rapidly from the tissues between 7 and 14 days, and has disappeared completely from the site by 21 days. Statement that DEPC disappears from the site by day 21 can still only be stated for the guinea pig i/d part of the study which was followed up till day 21. Other studies are not followed up after day 7 or 14.

Regarding MPI-947-041, a study to compare PK of SKY0402 manufactured by two processes (decant vs. non-decant, test vs. reference) after local infiltration in male dogs: great variability in individual PK parameters can be seen in both group of dose animals – T_{max} ranges from 0,5-96 h. Very high initial bupivacaine peaks are seen immediately after administration, which is not desirable for a depo product. Decanted SKY0402 was not bioequivalent to non-decanted SKY0402 at the level of 80 to 125%.

Regarding MPI-947-040, a study to evaluate the pharmacokinetics (PK) of SKY0402 (decanted process) after local infiltration in a surgical repair model ("surgical wound") compared to "normal tissues" (test vs. reference), Great variability in individual PK parameters can be seen: T_{max} ranges from 1 to 48 hours.

Overall applicability of this study is questionable because the applicant concluded that decanted and non-decanted process is not bioequivalent in dogs, yet, surgical model is performed with decanted model even though non-decanted model is presented for MAA. Inguinal hernia model is chosen for "surgery model" to cover various indications including hernia repair, mastectomy, and Caesarean section in humans. Assessor is of the opinion that this is not an appropriate surgery model because inguinal hernia presents protrusion of an organ or tissue through a natural opening in the abdominal wall - inguinal canal. During the staged surgery, it was only necessary to cut through the skin, bluntly reach peritoneum of the dogs and put a closure on fascias, aponeuroses and inguinal ligament. This is not a representative procedure for all clinical procedures, stated by the applicant, in which incision of deeper and other types of tissues must be done (caesarean section, mastectomy, and orthopaedic surgeries).

In the study MPI-947-040 higher AUC and C_{max} are seen in the surgery model. The applicant provided a scientific discussion on possible reasons for higher C_{max} and AUC seen in surgery models in dogs in comparison with intact skin. Among possible physiological changes that could potentially lead to increased absorption of bupivacaine are: injured cells which release inflammatory chemical signals leading to vasodilatation, increased blood flow, temperature increase, leaky endothelial lining of local blood vessels allowing neutrophils, macrophages and fluid to move into interstitial tissue. Recruitment of dendritic cells and macrophages and extracellular proteases released from neutrophils could potentially increase the rate of breakdown of lipid nanoparticles.

Non-clinical surgery model presented for hernia repair, mastectomy, and Caesarean section in humans but no models for surgical procedures in which bone tissue is affected, as these are prevalent procedures presented in clinical dossier (bunionectomy, total knee arthroplasty, total shoulder arthroplasty). The applicant did not expect any differences in PK when bone tissues are affected by surgery. Bone tissues have no significant contribution to bupivacaine metabolism pathways and it is not expected that the bone tissue would significantly contribute to the metabolism, distribution or clearance of bupivacaine.

The applicant conducted several studies to compare PK profiles of newly manufactured Exparel lots. Tested lots were manufactured with some process modifications or were stored at different storage conditions. These studies cannot be considered as proper basic PK studies as their only aim was to verify new lots based on their PK profile in comparison with control lots in research and development phase of the drug. Therefore, assessor is of the opinion that these studies do not significantly contribute to understanding of basic PK of this product and can be considered only as supportive studies. As such, they should be presented in Other pharmacokinetic studies and should not be assessed in depth. However, as the applicant did enclose these studies in basic pharmacokinetic part, there are some points regarding their conduction and interpretation that assessor wishes to point out. It is not clear why there was such a big difference in the concentration of control and test lots in the study 041018-D0402-534 (control 25mg/ml that is 36 mg/kg compared to Test lots 14 and 15 mg/ml that is 20 and 21 mg/kg). It is mentioned that difference between PK profile of control and tested lots could be result of this, but it does not answer the question why various concentrations were applied or why then the study was not repeated with equivalent or similar concentrations between the groups. Despite groups had been administered with different concentrations they had similar C_{max} values. It is not clear if new lots administered in same concentration as control lot would not produce much higher C_{max} (and potentially produce toxic effect of bupivacaine). Also, in study RES-050502-D0402-608 where effects of different storage conditions were observed, there was big difference in concentrations of control and tested lots.

Some results of these studies show that PK profiles of tested lots differ from control. The applicant did not explain how and whether these findings affected further drug development: was manufacturing process modified, and if so, how; or were tested clinical batches further used in clinical trials after these non-clinical studies were performed? In cases like this it is possible for applicant to refer to quality or clinical part of dossier in order to explain findings of non-clinical studies. But in this case, that was not done in any part of non-clinical documentation for this application. Without knowing what the

consequences were of their results, it is hard to evaluate the weight of these studies. The only thing that can be concluded is that process change and storage conditions may influence the *in vivo* release profile of bupivacaine. Furthermore, the applicant did not define PK parameters which would be desirable for this drug product. In some studies, due to difference in applied concentrations of bupivacaine, systemic exposure was so low that is questionable if those concentrations would even produce pharmacological effects of drug substance. Link between PK parameters and pharmacological effect of bupivacaine is not discussed in nonclinical or clinical part of dossier.

In summary, these non-GLP studies evaluated the plasma bupivacaine PK of different lots of Exparel. It was shown that variety of absorption characteristics impact the PK response, including species, dose, formulation, route of administration, vascularity of the administration site and other factors at site of administration. In addition, process variants and effects of storage and temperature can also change PK profile of Exparel.

AUC and C_{max} for DepoBupivacaine in study RES-0703-D0402-026 is very low. In addition, T_{max} for DepoBupivacaine is very variable. Great interindividual differences in PK parameters can be seen for Depo formulation. The applicant states that the low AUC is explainable by the fact that it is the first study performed by a new preclinical scientist.

Distribution

In-depth distribution studies were not performed as part of the nonclinical program for Exparel as the distribution of bupivacaine is considered well known and as there is long standing experience on the therapeutic use in Europe. Factors that may affect distribution of bupivacaine from the site of injection among other factors include the dosage form, release rate, plasma and tissue protein binding and metabolic activity.

The only distribution study that was conducted using Exparel was study to determine whether Exparel liposomal particles are sequestered within the blood cell fraction from beagle dogs following centrifugation. Distribution of Exparel within blood was compared to distribution of IR bupivacaine. There was no difference in the distribution of bupivacaine in blood between the dogs treated with Exparel comparing to IR bupivacaine. As IR bupivacaine is widely used substance, provided review of relevant published references on bupivacaine distribution is considered sufficient to justify distribution of Exparel.

Metabolism

Bupivacaine is widely used substance with metabolism well documented in the literature. Applicant provided short review on its metabolism citing published literature references enclosed in module 4. No metabolism studies are deemed necessary.

Bupivacaine in other drug products is usually stored below 25°C as a precautionary measure to prevent bupivacaine from degradation. The applicant claims that they conducted a thermal degradation study on Exparel and bupivacaine phosphate at 40°C for 4 days using the analytical procedure for bupivacaine degradation products. A full report on this study is not included in the applicant's response as the applicant said that it is only being finalised. A table with percent of impurities content in control and degraded samples for Exparel and Bupivacaine phosphate was presented. Impurity profiles of control and samples that were placed under thermal stress at 40°C for 4 days were completely the same. Since elevated temperature (up to 40°C) did not have an effect on degradation of bupivacaine, it could be expected that degradation of bupivacaine inside Depo formulation would not alter when Exparel is applied in patient's body.

Interactions

PK data from study [S08668](#) cannot be sorted considering great interindividual differences in PK parameters or possible PK interactions and no firm conclusion can be drawn from this study S08668. PK parameters are not dose related, as it was seen also in previous studies. PK interaction between bupivacaine HCl and DepoBupivacaine, regardless of concentration, ratio or time slot between drugs, cannot be excluded.

Maximum dose of bupivacaine administered in different formulations was 4-5 mg/kg in total (2+1 or 4+1). Maximum recommended dose for bupivacaine HCl local infiltration in swine in practice is 5 mg/kg (*Swindle and Smith, 2016.*). This is in contrast with PK studies with other species, where bupivacaine was usually overdosed. No studies with Exparel are done with 5 mg/kg dose of single product DepoBupivacaine or bupivacaine HCl in swine, no comparison can be done.

It was noted in PK studies in dogs that there is a model-dependant PK profile of Exparel (alteration of PK parameters when administered into wound). It is reasonable to presume that study **S07607** does not present a firm evidence of absence of PK interactions since there is a possibility of alteration of PK parameters when epinephrine and lidocaine are administered into wound. Discussion on results of S07607 study is presented. This study formed the basis of the recommendation that lidocaine could be administered with Exparel after a 20 min delay. The applicant has removed the statement regarding the use of Exparel in conjunction with epinephrine from the proposed SmPC. There is still no dose adjustment for lidocaine or Exparel in the proposed SmPC. It can be presumed that the applicant does not consider dose adjustments necessary if the 20 minutes period is respected. In the responses to clinical questions, a report on serious adverse reactions is presented collected from postmarketing data in countries where Exparel is already marketed. It can be seen that a number of adverse effect are caused by concomitant use of lidocaine, mostly due to medical error, some attributed to lidocaine and/or epinephrine, some attributed to Exparel.

Presented non-clinical PK interaction study [S08668](#) cannot be taken as a firm evidence of absence of PK interaction between bupivacaine HCl solution and DepoBupivacaine when premixed in the same syringe. No new non-clinical data were submitted. According to the applicant, the Study S08668 conducted in pigs had an exploratory objective to evaluate interaction potential when Exparel and IR bupivacaine were administered at various ratios but not to test the maximum doses of two products that could be co-administered. In vitro compatibility study by Kharitonov (2014) showed that admixing Exparel and IR bupivacaine in ratio 2:1 or higher should not affect release of bupivacaine from the liposomes at room temperature. This suggests that no significant interaction is expected for the admixture prepared in the syringe. Refer to assessment of clinical issues.

PK parameters following intravenous or subcutaneous administration of Exparel or IR bupivacaine in dogs were compared. Results clearly show desirable prolonged and more uniform PK profile of Exparel.

Even though concentration of Exparel that was applied SC was multiple times higher, due to slower release from liposomes, C_{max} in group that it was administered was never as high as C_{max} in group that had Exparel administered intravenously. Prolonged release could also be seen in significantly longer T_{max} in the same group.

Other studies

The applicant states that regarding absorption, distribution, metabolism, and excretion of the phospholipid (DOPC, DEPC, and DPPG) and neutral lipid (cholesterol, triolein, tricaprylin) components of the DepoFoam matrix, since these are all naturally occurring or synthetic analogues of common lipids, the metabolic fate of these excipients is expected to be similar to that of endogenous lipids. The applicant presented an overview of expected absorption, metabolism and excretion of lipid components of DepoFoam. The metabolism and excretion of DepoFoam can theoretically be described based on an

understanding of the biochemistry of its individual components but the rate of absorption of lipid materials is different from and cannot be compared to simple subcutaneous injection of individual lipid components. DepoFoam remains on the site of application for a period longer than 28 days, but not in the original form. It is stated that tricaprylin becomes a liquid oil at body temperature leaving particles for partition into the surrounding tissues. Particles are then destabilised. If tricaprylin leaves DepoFoam shortly after administration, liposomes reorganise and their further excretion is delayed but this mechanism is not completely understood. It is presumed that all individual components follow lipid metabolism pathways.

The study QPS-137N-0401 objective was to determine the tissue distribution of DEPC and DEPC related material following a single, subcutaneous (SC) administration of a DepoFoam formulation containing [¹⁴C-labelled DEPC] to male, pigmented rats using quantitative whole-body autoradiography (QWBA). The applicant states, that quantitative whole-body autoradiography was used to evaluate the tissue distribution of DEPC (and metabolites). There are no data provided regarding metabolites of DEPC. DEPC is expected to follow the lipid catabolism pathways similar to a natural fatty acid. As DEPC is a synthetic homolog of natural lipid DOPC, explanation for possible metabolism of DEPC compared with DOPC is acceptable.

Tissue distribution of DepoFoam-bound bupivacaine following systemic exposure (e.g. following absorption after local application or following inadvertent systemic iv or ia application) has not been evaluated. Although the tissue distribution of DepoFoam-bupivacaine following systemic exposure was not formally evaluated, pharmacokinetic evaluations of Exparel following IV or IA administration were compared with immediate release (IR) bupivacaine in dogs (Study 504333). Since the pharmacokinetics of bupivacaine in Exparel following IV or IA administration in dogs was similar to IR bupivacaine, there is likely no significant difference in the tissue distribution of bupivacaine is expected. The distribution of bupivacaine is well known as it has been extensively characterised in the scientific literature and there is long standing experience on the therapeutic use with approved bupivacaine products. In addition, essentially little or no liposome-encapsulated bupivacaine circulating in the vasculature after SC administration of Exparel.

Reproductive toxicity and tissue distribution of DepoFoam bound bupivacaine to foetal tissues following systemic exposure (e.g. following absorption after local application or following inadvertent systemic iv or ia application) have not been evaluated. Pharmacokinetic evaluations of Exparel following intravenous or intraarterial administration were compared with immediate release bupivacaine in dogs, which demonstrated no significant differences in the pharmacokinetics of the two thus suggesting no significant differences in their tissue distribution. Based on the obtained data, it is most likely that the reproductive toxicity of Exparel is similar or even lower than that of IR bupivacaine due to the lower systemic maximal concentrations of bupivacaine when administered in the encapsulated form.

Toxicology

Single dose studies

Exparel, when administered in a single dose SC or as a nerve block to rats, dogs and rabbits, shows a very low or no acute toxicity. Nevertheless, it has a local effect on skin and subcutis, which is not seen with Bupivacaine HCl. In all presented studies, various local effects are reported, predominantly local (granulomatous) inflammatory changes on the injection sites. This is an effect not seen with simple bupivacaine HCl solution and it should be attributed to the liposomal particles in the drug product.

Three studies were performed using SKY Placebo intravenously: two dose-range finding studies and one expanded toxicity study of Placebo in rats. In the last study, one animal died in the 1 mL/kg group, immediate postdose with signs of salivation, decreased activity, breathing shallow and slow, black material around nose, righting reflex lost. Macroscopically no findings. The cause of death could not be

determined but was considered test article-related. Clinical observations occurred sporadically and isolated or only a few animals with no clear relationship to the test article. These included, among others, clinical symptoms very similar to those of the animal died on study with no other macroscopic and microscopic findings: salivation, red material around nose, rapid and/or shallow breathing, and decreased activity. Even though, symptoms did not occur in one but rather in several animals, assessor is of the opinion that the dose level of 0.5 ml/kg cannot be considered a NOEL since symptoms similar to those occurred in dead animal in high group, occurred also in lower groups but with no fatalities. In tox studies with SKY0402 administered IV and IA, more severe effects were noted with IA administration. Within two of these studies (in dogs) a board-certified veterinary cardiologist conducted a qualitative review of ECGs obtained twice prior to each dose (at least 30 minutes apart) and at immediately post dose (within 2 minutes), 10, 30 and 90 minutes post dose following the intravenous or intra-arterial injection of escalating doses of Exparel or Bupivacaine HCl in dogs. There was no effect of the intravenous or intra-arterial injection of escalating doses of Exparel or Bupivacaine HCl on qualitative ECG parameters. In the study 694604 Animal 3501 was not euthanised after having severe clinical signs of toxicity after first dose (decreased and increased activity, convulsions, tremors, lying on side, decreased muscle tone, weak, pale skin, salivation, respiratory rate irregular, urination and defecation during examination) which raises an ethical concern. Animal was dosed three more times. Difference in clinical signs after administration of same dose IV Exparel (9 mg/kg) are noted: one animal had to be euthanised (no 2502) due to severity of symptoms after the first administration and the other (2501) had only moderate symptoms after repeated dose of IV Exparel.

Number of animals is too small to determine an MTD. Study 694609 is a dose-range finding study limited in scale and scope, intended for future dose-selection. Animal, which tolerated 9 mg/kg intravenously, received a single dose of 4.5 mg/kg three days before. The applicant argues that this animal is probably tolerant to bupivacaine, or the dose is near the limit of tolerability. Interindividual differences and variability in response is acknowledged.

Intravenous administration of bupivacaine at 1.5 mg/kg and intra-arterial administration of Exparel at 3.0 or 4.5 mg/kg resulted in adverse clinical signs including convulsions, lying on side, and decreased muscle tone. Intravenous administration of bupivacaine at 0.75 mg/kg, as well as intravenous administration Exparel at 1.5 mg/kg resulted in less severe clinical signs of emesis, increased or decreased activity, tremors, and uncoordination in individual animals. All clinical signs were transient and had no clinical or anatomic pathology correlates. NOEL for intra-arterial administration of bupivacaine was considered to be 0.1 mg/kg. No NOAEL could be determined for intra-arterial administration of Exparel. In conclusion, Exparel is not to be administered IV or IA since the effect of IV and IA administration is not known except that IA administration is potentially fatal when administered in sufficient amount into carotid arteries. Exact pathological mechanism is not known since this is not discussed; no pathologic correlations are found.

Administering test product via right carotid artery is not representative of clinical situation. Test product administered intra-arterial into carotids is delivered to the head of animals, whereas in clinical setting, if the product is to be administered IA by mistake, it will most probably be administered distally, into arteries of limbs or abdomen. It is confirmed that administration of Exparel in carotid arteries is toxic and can be lethal. The applicant provided a short overview of two possible scenarios if Exparel is to be administered intravascular, with no distinction between intravenous and intra-arterial administration. Following accidental administration in a peripheral artery away from the CNS, it is expected that the plasma levels and potential untoward effects would be similar to what is seen following comparable doses in accidental intra-venous administrations.

No relevant conclusion can be drawn out of intrathecal and epidural studies at this time point since epidural/intrathecal route is not an expected route of administration in clinical setting.

In the repeat dose toxicity studies with Exparel, the applicant set NOAELs not taking into consideration local effects as adverse. SKY0402 does not produce a notable and significant systemic toxicity except in rabbits, which are most sensitive of species selected for repeat dose testing and convulsions are seen with SKY0402 9 mg/kg similar to IR bupivacaine 9 mg/kg.

Repeat dose studies

Significant findings in repeat dose studies are all related to local findings: red discoloration and swelling/thickening of injection sites, microscopic findings of haemorrhage and neovascularisation, minimal to moderate number of vacuolated macrophages, giant cells, granulomatous inflammations in the subcutis and mineral deposits. The subcutaneous granulomatous inflammation and mineralisation associated with SKY0402 seen in repeat dose toxicity studies is not considered reversible since it was observed in recovery animals, except for the monthly local femoral nerve block.

The last study (Monthly local femoral nerve block injections, Beagle dogs) has a dosing schedule with administrations so infrequent, it can be almost considered a single dose toxicity study, especially since the applicant is constantly stating that the drug is cleared by 28 days. Nevertheless, local granulomatous inflammation is noted here also.

SKY0402 Placebo material does not produce systemic toxicity but local reactions are consistently found and they include: mild to moderate chronic panniculitis, granulomatous inflammation, thickening of injection sites, accumulations of vacuolated macrophages, mineralisation, with only oedema and haemorrhage not found in recovery animals.

The subcutaneous granulomatous inflammation and mineralisation associated with SKY0402 seen in repeat dose toxicity studies is not considered reversible since it was observed in recovery animals. The applicant presents an overview of all noted granulomatous inflammation processes in non-clinical studies and argues these findings likely involve normal lipid clearance processes; it was not considered adverse and resolves over time. From the applicant's presentation of all granulomatous inflammatory changes in non-clinical studies, it can be concluded that complete reversal of changes can be expected somewhere between one and three months after application. It is not considered to be a concern for human, particularly with an acute exposure regimen. As for the issues related to the observed sex-differences in terms of higher chronic inflammation rates in female rats in SC toxicity study, the applicant provides a meaningful clarification on the study data interpretation by explaining that the size of the measured biological effect in females was negligible – i.e., the severity of the inflammation was minimal in most of the cases. The applicant justifies that despite the observable difference between sexes, it is not considered to represent true sex differences but rather biological variation.

Toxicokinetic

Toxicokinetic analysis was done within several toxicity studies. Since the collected PK data is very variable between studies (because of different routes of administration/study designs and doses) and individual animals, assessor was not able to make a single table with all TK values. It has to be emphasised that drawing statistical analysis for this kind of messy data in small groups of animals is highly questionable. This is also in line with ICH S3A Guideline – Note for Guidance on Toxicokinetics: the assessment of systemic exposure in toxicity studies: in some cases, the data of individual animals may be more important than a refined statistical analysis of group data.

Also, it was not possible to make an interspecies comparison and comparison with doses in humans since a too variable range of doses are used in clinical setting (see clinical PK AR) and in non-clinical studies.

In MPI-947-030 study, T_{max} ranges from 1 to 48 hours. Systemic exposure is lower when rabbits are given higher dose of bupivacaine encapsulated in liposomes in comparison to IR bupivacaine. This is a desirable profile for a depo product, but a very variable T_{max} can be seen and C_{max} was notably higher

in one animal receiving SKY0402 – animal no 172, a female, had a 10 times higher exposure at T_{max} compared to other 3 animals in the same group. Considering small groups of animals, this effect has to be noted and taken as a possibility of sudden disruption of liposomes and release of higher amount of bupivacaine in bloodstream.

C_{max} seems to be higher after field block than after nerve block in rabbits. In addition, T_{max} is somewhat lower in field block group, meaning bupivacaine is absorbed faster and in higher quantities in field block than in nerve block site.

In the MPI-947-029 study, systemic exposure is generally lower when dogs are given bupivacaine in the same or higher dose, encapsulated as SKY0402, in comparison to IR bupivacaine. This is a desirable effect for a depo product. High interindividual differences are noted again. Animal no. 111 had a similar C_{max} with the same dose of IR bupivacaine and Depo Bupivacaine (1450 ng/mL IR bupi; 1230 ng/mL SKY0402) and substantially higher AUC 0-96h exposure in comparison with IR bupivacaine and similar AUC 0-96h to high dose SKY0402 group (21800 ng·hr/ml). Animal no. 151 had ten times higher C_{max} compared to other animals in the same group. Same effect is seen in animal no. 160. While in animal no 172 a very low C_{max} is seen compared to other animals in the same group.

AUC_{0-96h} in Exparel group after peripheral nerve block ranges from 13600 to 30400 ng·hr/ml and 12700 to 42800 ng·hr/ml respectively. T_{max} is lower after SC infiltration. C_{max} and AUC are higher after peripheral nerve block. Meaning that after SC infiltration a high initial peak of bupivacaine in blood can be expected with subsequent slower release and lower blood concentration.

In the study MPI-947-036 (twice weekly dosing SC in rabbits) TK data suggests that each dose of SKY0402 was not cleared completely before the next dose was administered. There is noted different susceptibility to bupivacaine in rabbits, including higher sensitivity to toxic effects.

In the study MPI-947-037 (twice weekly dosing SC in dogs) TK data suggests that each dose was cleared almost completely before the next dose was administered. There is no cumulative toxicity reported in repeat dose toxicity study dogs.

Genotoxicity

According to presented literature, bupivacaine is not genotoxic but a potential metabolite of bupivacaine, 2,6-xylidine, is a weak mutagenic agent *in vitro* and has genotoxic characteristics *in vivo* under certain conditions. This issue is addressed in the impurities part of AR as 2,6 xyloidine is also an impurity in this drug product. SKY0402 Placebo did not show genotoxic potential in performed studies. Exposure in the *in vivo* test is considered adequate.

Reproductive and developmental toxicity

From the standard battery of reproductive and developmental studies performed with placebo, it can be concluded that SKY0402 Placebo does not have an effect on reproduction and development.

Local tolerance

Study RES-0702-D0402-044: Incidence of local tissue reactions on the site of administration is greater in DepoBupivacaine and Placebo groups. A single SC injection of DepoBupivacaine at concentrations up to 25 mg/kg was well tolerated systemically, but was associated with histopathological changes at the injection site, typical of foreign body reactions. Necropsies were done 13 days post dosing.

Study MPI 947-004: All changes directly associated with the skin incision and foreign material (hair, staples): discoloration of the injection site, mild to moderate inflammation, epithelial hyperplasia and fibroplasia. No effects observed at the intra-articular and femoral nerve sites. No major group differences that would indicate local toxicity of DepoBupivacaine in all three injection sites.

It is noted that there was only one incision site per one rabbit, meaning no control was used for incision site leading to the fact that only 4 rabbits received SKY0402 into a 2.54 cm long incision site. This is a quite small number meaning there is a possibility that SKY0402 related effects could not be grasped with study design of 4/4 rabbits receiving SKY0402/bupivacaine HCl. Also, other dosing sites were not subjected to surgery prior to administration which is not a representative clinical situation where an incision is done through various tissues.

Dose levels recommended for rabbits are obviously exceeded per one dose site and extremely in all dosing sites together, which is also the reason for the death of two animals in the second group. Since this is a "stand alone" local tolerance study, the actual concentration of active substance to be used in humans should have been tested, not the toxic doses. In addition, testing in different sites on the same animal is permissible if the systemic tolerance permits, which is not the case in this study.

Animal welfare should be one of the highest priorities when investigating local tolerance (EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*) and this study raises an ethical concern. The applicant states that mortality in this study was unfortunate, unexpected and believed to be due to an accumulation of exposure from all three administration sites. It is emphasised that the study was conducted in 2002. While the recent guidance for local tolerance studies is published in 2016.

Study MPI 947-013: Total bupivacaine dog dose was reasonably administered and not overdosed. Femoral nerve area and intra-articular injection were administered without previous surgical procedure. No effect on femoral nerve and stifle joint were noted and no differences were noted between groups. It has to be emphasised that this is not a completely representative clinical situation where intra-articular and nerve block will be administered during procedures, which involve incisions through various tissues. Animal 211 is the only animal with findings in the intra-articular site and the one of two animals with severe oedema on incision sites treated with placebo. Animal 208 pulled out staples from the wound. Severe oedema was also found in this animal's placebo treated wound.

In the single dose toxicity studies in all presented studies, various local effects are reported, predominantly local (granulomatous) inflammatory changes on the injection sites. This is an effect not seen with simple bupivacaine HCl solution and it should be attributed to the liposomal particles in the drug product.

In the repeat dose toxicity studies significant findings are all related to local findings: red discoloration and swelling/thickening of injection sites, microscopic findings of haemorrhage and neovascularisation, minimal to moderate number of vacuolated macrophages, giant cells, granulomatous inflammations in the subcutis and mineral deposits. The subcutaneous granulomatous inflammation and mineralisation associated with SKY0402 seen in repeat dose toxicity studies is not considered reversible since it was observed in recovery animals, except for the monthly local femoral nerve block.

In the repeat dose toxicity study with SKY0402 Placebo material does not produce systemic toxicity but local reactions are consistently found and they include: mild to moderate chronic panniculitis, granulomatous inflammation, thickening of injection sites, accumulations of vacuolated macrophages, mineralisation, with only oedema and haemorrhage not found in recovery animals.

Overall, findings on incision wound sites in local tolerance studies, findings from single dose toxicity studies of SKY0402, repeat dose toxicity studies with SKY0402 and SKY0402 Placebo material is indicative of local irritative potential of liposomal particles to subcutaneous tissue. Even with single application but especially with repeat/prolonged exposure, presence of exogenous lipids seems to be a nidus for the development of foreign body type of reaction in surrounding tissues which is not reversible even after a period of one month. It seems possible that prolonged or repeated application of Exparel could cause dystrophic changes at the injection site.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical dossier is sufficient to support the Marketing Authorisation application for Exparel.

2.5. Clinical aspects

2.5.1. Introduction

GCP

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.

The applicant provided efficacy results from the 6 Phase 2, randomised, double-blind, multicentre, dose finding/ranging studies and 11 Phase 3, randomised, double-blind, multicentre studies which are grouped by the intended effect of Exparel to produce local analgesia or regional analgesia:

- Local analgesia (field block) studies: 201 and 207 (hernia repair); 209, 312, and 316 (haemorrhoidectomy); 208, 311, and 331 (TKA); 317 (bunionectomy); 210 (breast augmentation); 329 (third molar extraction); and 411 (caesarean section).
- Regional analgesia (peripheral nerve block) studies: 203 (bunionectomy); 323 and 326 (TKA); 327 (TSA/RCR); and 322 (thoracotomy).

Local analgesia studies where Exparel was administered as a field block are summarised in Table 2. There were five Phase 2 studies and seven Phase 3 studies. The Phase 2 studies evaluated Exparel doses ranging from 66 mg to 532 mg and were used to inform dosing for the Phase 3 studies. The Phase 3 studies assessed the efficacy and safety of Exparel doses ranging from 106 mg to 532 mg.

Table 2: Key Study Characteristics of Phase 2 and Phase 3 Local Analgesia Studies

Study; Study Phase	Surgery Type	Exparel Dose(s) (mg)	Control Dose (mg)	N ^a EXP : Control	Primary Efficacy Endpoint
Placebo-controlled studies					
316; Phase 3	Haemorrhoidectomy	266	Placebo	94 : 93	AUC NRS-R ₀₋₇₂
317; Phase 3	Bunionectomy	106	Placebo	97 : 96	AUC NRS-R ₀₋₂₄
329; Phase 3	Third molar extraction	133	Placebo	99 : 51	AUC NRS-R ₀₋₄₈
Active-controlled studies					
208; Phase 2	TKA	133, 266, 399, 532	IR bupivacaine 133	103 : 35	AUC NRS-A ₀₋₉₆
311; Phase 3		532	IR bupivacaine 177	108 : 110	AUC NRS-A ₀₋₇₂
331; Phase 3		266 + IR	IR bupivacaine 89	70 : 69	AUC of VAS ₁₂₋₄₈ and the total opioid

Study; Study Phase	Surgery Type	Exparel Dose(s) (mg)	Control Dose (mg)	N^a EXP : Control	Primary Efficacy Endpoint
		bupivacaine 89			consumption (in IV MED) from 0 to 48 hours
209; Phase 2	Haemorrhoidectomy	66, 199, 266	IR bupivacaine 66	75 : 25	None
312; Phase 3		266	IR bupivacaine 89	99 : 99	AUC NRS-R ₀₋₉₆
210; Phase 2	Breast augmentation	133, 266	IR bupivacaine 66	20 : 20	None
201; Phase 2	Hernia repair	155, 199, 266, 310	IR bupivacaine 89	50 : 26	Time to first postsurgical use of supplemental pain medication (opioid or non- opioid) for surgical wound pain
207; Phase 2		93, 159, 306	IR bupivacaine 93	73 : 25	None
411; Phase 3	Caesarean section	266 + IR bupivacaine 44	IR bupivacaine 44	71 : 65	Total opioid consumption (in IV MED) from 0 to 72 hours

^a Sample size reflects the primary analysis population for each respective study; all doses for Exparel and IR bupivacaine are expressed in the form of bupivacaine free base equivalent.

AUC: area under the curve; EXP: Exparel; IV: intravenous; MED: morphine equivalent dose; NRS-A: numerical rating scale with activity; NRS-A₀₋₇₂: numerical rating scale with activity from 0 through 72 hours; NRS-A₀₋₉₆: numerical rating scale with activity from 0 through 96 hours; NRS-R₀₋₂₄: numerical rating scale at rest from 0 through 24 hours; NRS-R₀₋₄₈: numerical rating scale at rest from 0 through 48 hours; NRS-R₀₋₇₂: numerical rating scale at rest from 0 through 72 hours; NRS-R₀₋₉₆: numerical rating scale at rest from 0 through 96 hours TKA: total knee arthroplasty; VAS₁₂₋₄₈: visual analogue scale from 12 hours to 48 hours

Regional analgesia studies where Exparel was administered as a peripheral nerve block are summarised in Table 3. There were two Phase 2 studies and four Phase 3 studies. The Phase 2 studies evaluated Exparel doses ranging from 67 mg to 310 mg and were used to inform the dosing for the Phase 3 studies. The Phase 3 studies assessed the efficacy and safety of Exparel 133- and 266-mg doses.

Table 3: Key Study Characteristics of Phase 3 Regional Analgesia Studies

Study ID	Surgery Type	Exparel Dose(s) (mg)	Control Dose (mg)	N ^a EXP : Control	Primary Efficacy Endpoint
Active-controlled study					
203	Bunionectomy	155, 199, 310	IR bupivacaine 111	38 : 20	Time to first use of supplemental pain medication
Placebo-controlled studies					
322	Thoracotomy	266	Placebo	94 : 91	AUC NRS-R ₀₋₇₂
323 (Part 1) ^b	TKA	67, 133, 266	Placebo	70 : 24	AUC NRS-R ₀₋₇₂
323 (Part 2) ^b	TKA	266	Placebo	92 : 91	AUC NRS-R ₀₋₇₂
326	TKA	133 and 266	Placebo	151 : 79	AUC VAS ₀₋₇₂
327	TSA/RCR	133 and 266	Placebo	84 : 71	AUC VAS ₀₋₄₈

^a Sample size reflects the primary analysis population for each respective study.

^b Study 323 was a combined Phase 2 (Part 1) and Phase 3 (Part 2) study.

AUC: area under the curve; EXP: Exparel; NRS-R₀₋₇₂: numerical rating scale at rest from 0 through 72 hours; RCR: rotator cuff repair; TKA: total knee arthroplasty; TSA: total shoulder arthroplasty; VAS₀₋₄₈: visual analogue scale from 0 to 48 hours; VAS₀₋₇₂: visual analogue scale from 0 to 72 hours

A rationale regarding selection of the surgical procedures has been provided. According to the applicant the surgical procedures selected for the clinical studies are representative of surgeries that would be expected to lead to moderate-to-severe pain of sufficient duration to benefit from a long acting local anaesthetic and where sustained management of acute pain is traditionally managed with a CPNB or opioids. The surgical procedures included models of both somatic pain (e.g., third molar extraction, bunionectomy, major orthopaedic surgery) as well as models of mixed somatic/visceral pain (e.g., abdominal/thoracic surgery).

Different doses were evaluated and compared with saline placebo and IR bupivacaine (as standard of care).

Of note, early in the development program, the bupivacaine dose delivered by Exparel is expressed as bupivacaine HCl equivalents. However, after 2011, at US FDA's request, the bupivacaine dose delivered by Exparel is expressed as bupivacaine free base equivalents. The conversion factor from bupivacaine HCl equivalents to bupivacaine free base equivalents is as follows:

0.886 mg bupivacaine free base = 1.0 mg bupivacaine HCl equivalent.

2.5.2. Pharmacokinetics

The active pharmaceutical ingredient in Exparel is bupivacaine, an amide-type local anaesthetic, which is commercially available as immediate-release (IR) bupivacaine and has been marketed in Europe and worldwide for more than 50 years.

Exparel is bupivacaine encapsulated in the DepoFoam® drug delivery system. The prolonged release allows reduced peak plasma concentrations. Once released from the liposomes, bupivacaine absorption and disposition is expected to be the same as for other bupivacaine hydrochloride solution formulations. Published literature was used to support bupivacaine disposition and drug interactions.

Clinical pharmacokinetic data were obtained in target patient population in ten clinical studies (4 Phase 2 and 6 Phase 3). Five studies were conducted to support the clinical pharmacology of Exparel as a field block to produce local analgesia and five other studies were conducted to support the clinical pharmacology of Exparel as a peripheral nerve block to produce regional analgesia. Exparel doses evaluated in these studies ranged from 67 mg to 532 mg of bupivacaine. Additionally, several healthy volunteer studies were conducted where Exparel was administered mainly subcutaneously.

Full PK profiling was performed in all PK studies. Two population PK analyses were conducted, one to describe pharmacokinetics of Exparel in the field block and the other in the peripheral nerve block setting.

Table 4: Key Exparel Clinical Pharmacology Studies

Study number	Study objective	Study design	Study drug, Dose, Route of administration	Number of subjects enrolled	Type of subjects
108	Comparative BA, safety and tolerability of three lots of Exparel	Randomised, double-blind, two-period, crossover study	Exparel 266 mg (20 mL) Subcutaneous	30 (18 received Lot A, 19 received Lot B, and 20 received Lot C)	Healthy subjects
116	BE, safety and tolerability of two lots of Exparel	Randomised, double-blind, three-period, three-sequence, crossover BE study	Exparel 266 mg (20 mL; one lot each from two different manufacturers) Subcutaneous	48 (16 in each treatment sequence)	Healthy subjects
119	BE, overall safety and tolerability of three lots of Exparel	Randomised, double-blind, three-period, three-sequence, crossover BE study	Exparel 266 mg (20 mL; one lot with <i>in vitro</i> release characteristics within specification and two lots with <i>in vitro</i> release characteristics	46 (16 in A/A/B, 15 in A/B/A, and 15 in B/A/A)	Healthy subjects

			out-of-specification) Subcutaneous		
002	PK, PD, and safety of Exparel relative to IR bupivacaine	Randomised, double-blind, parallel group, dose-escalating study	Exparel 66 mg (15 mL) Exparel 111 mg (15 mL) Exparel 133 mg (15 mL) Exparel 155 mg (15 mL) IR bupivacaine 66 mg (15 mL) Perineural nerve block	6 7 6 6 12	Healthy subjects
113	PK and safety of Exparel	Open-label cohort study	Exparel 266 mg (20 mL; Day 1) Exparel 266 mg (20 mL; on Day 1 and Day 4) Exparel 266 mg (20 mL; on Day 1 and Day 3) Exparel 266 mg (20 mL; on Day 1 and Day 2) Exparel 266 mg (20 mL; 2 doses on Day 1) Subcutaneous	12 12 12 12 12 12	Healthy subjects
117	PK, safety, tolerability, and efficacy of Exparel	Open-label study	Exparel 266 mg (20 mL expanded in volume with 40-280 mL normal saline) Field block	14	Patients undergoing open posterior spinal fusion or reconstructive surgery

118	PK, safety, and tolerability of Exparel	Open-label cohort study	Exparel 266 mg (20 mL expanded in volume with 20 mL normal saline) Exparel 266 mg (20 mL expanded in volume with 10 mL normal saline) Perineural posterior intercostal nerve block	5 (terminated early due to slow enrolment)	Patients undergoing posterolateral thoracotomy
110	PK and safety of Exparel	Open-label, parallel-group study	Exparel 266 mg (20 mL) Subcutaneous	18 (9 with normal hepatic function and 9 with moderate hepatic impairment)	Subjects with normal hepatic function or moderate hepatic impairment
<i>Local analgesia</i>					
316	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, parallel-group, placebo-controlled study	Exparel 266 mg (30 mL) Saline (placebo; 30 mL) Field block	95 94	Patients undergoing haemorrhoidectomy
317	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, parallel-group, placebo-controlled study	Exparel 106 mg (8 mL) Saline (placebo; 8 mL) Field block	97 96	Patients undergoing bunionectomy
329	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, placebo-controlled study	Exparel 133 mg (10 mL) Saline (placebo; 10 mL) Field block	105 57	Patients undergoing third molar extraction

201	Efficacy, safety, and PK of Exparel compared with IR bupivacaine	Randomised, double-blind, dose-escalating/ de-escalating, active-controlled study	Exparel 155 mg (40 mL)	12	Patients undergoing inguinal hernia repair
			Exparel 199 mg (40 mL)	12	
			Exparel 266 mg (40 mL)	12	
			Exparel 310 mg (40 mL)	14	
			IR bupivacaine 89 mg (40 mL)	26	
Field block					
208	Efficacy, safety, and comparative systemic bioavailability of Exparel compared with IR bupivacaine	Randomised, double-blind, parallel-group, active-controlled, dose-ranging study	Exparel 133 mg (60 mL)	28	Patients undergoing total knee arthroplasty
			Exparel 266 mg (60 mL)	25	
			Exparel 399 mg (60 mL)	26	
			Exparel 532 mg (60 mL)	25	
			IR bupivacaine 133 mg (60 mL)	34	
Field block					
<i>Regional analgesia</i>					
203	Efficacy, safety, and PK of Exparel compared with IR bupivacaine	Randomised, double-blind, dose-escalating/ de-escalating study	Exparel 155 mg (25 mL)	12	Patients undergoing bunionectomy
			Exparel 199 mg (25 mL)	12	
			Exparel 310 mg (25 mL)	14	
			IR bupivacaine 111 mg (25 mL)	20	
Perineural ankle nerve block					
322	Efficacy, safety, and PK of Exparel	Randomised, double-blind, parallel-group,	Exparel 266 mg (20 mL)	94	Patients undergoing posterolateral thoracotomy
				91	

	compared with placebo	placebo-controlled study	Saline (placebo; 20 mL) Perineural intercostal nerve block		
323	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, parallel-group, placebo-controlled, dose-ranging study	Part 1: Exparel 67 mg (20 mL) Exparel 133 mg (20 mL) Exparel 266 mg (20 mL) Saline (placebo; 20 mL) Part 2: Exparel 266 mg (20 mL) Saline (placebo; 20 mL) Perineural femoral nerve block	22 24 24 24 92 92	Patients undergoing total knee arthroplasty
326	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, placebo-controlled study	Exparel 133 mg (20 mL) Exparel 266 mg (20 mL) Saline (placebo; 20 mL) Perineural femoral nerve block	75 76 79	Patients undergoing total knee arthroplasty
327	Efficacy, safety, and PK of Exparel compared with placebo	Randomised, double-blind, placebo-controlled study	Exparel 133 mg (20 mL) Exparel 266 mg (20 mL) Saline (placebo; 20 mL) Perineural brachial plexus nerve block	69 15 71	Patients undergoing total shoulder arthroplasty or rotator cuff repair

Absorption

The systemic absorption of Exparel depends primarily on the rate at which bupivacaine is released from the liposome particles, which was designed to take place gradually over an extended time period. Several PK studies comparing Exparel with bupivacaine HCl were conducted. In general, lower C_{max} values and longer measurable plasma concentrations of Exparel compared to bupivacaine HCl were shown (studies 201 (hernia repair), 203 (bunionectomy) and 002 (ankle nerve block, HV)).

PK was also evaluated in a range of different surgical models covering both field block and nerve block administration at sites of different vascularity.

Descriptive statistics of pharmacokinetic parameters of representative Exparel doses in field block and peripheral nerve block are provided in the tables below.

Table 5: Summary of PK parameters for bupivacaine after administration of single dose of Exparel via field block

Parameters	Surgical Site Administration	
	Bunionectomy 106 mg (8 mL)	Hemorrhoidectomy 266 mg (20 mL)
	(N=26)	(N=25)
C _{max} (ng/mL)	166 (92.7)	867 (353)
T _{max} (h)	2 (0.5-24)	0.5 (0.25-36)
AUC _(0-t) (h•ng/mL)	5864 (2038)	16,867 (7868)
AUC _(inf) (h•ng/mL)	7105 (2283)	18,289 (7569)
t _{1/2} (h)	34 (17)	24 (39)

Table 6: Summary of PK parameters for bupivacaine after administration of single dose of Exparel via peripheral nerve block

Parameters	Peripheral Nerve Block (Surgery)			
	Femoral Nerve Block (Total Knee Arthroplasty)		Brachial Plexus Nerve block (Total Shoulder Arthroplasty)	
	133 mg (10 mL)	266 mg (20 mL)	133 mg (10 mL)	266 mg (20 mL)
	(N=19)	(N=21)	(N=32)	(N=32)
C _{max} (ng/mL)	282 (127)	577 (289)	209.35 (121)	460.93 (188)
T _{max} (h)	72	72	48	49
AUC _(0-t) (h•ng/mL)	11,878 (7,870)	22,099 (11,137)	11426.28 (7855)	28669.07 (13205)
AUC _(inf) (h•ng/mL)	18,452 (12,092)*	34,491 (5,297)*	12654.57 (8031)	28774.03 (13275)
t _{1/2} (h)	29.0 (24)*	18.2 (6.)*	11 (4)	15 (6)

Overall, while the PK profiles of bupivacaine released from Exparel vary between the two routes of administration at the maximum proposed dose of 266 mg, a consistent extended PK profile was observed in both proposed routes of administration. Regardless of the surgical procedure, each route of administration presents a distinct shape for the PK curve that is unique to each route. Differences in the PK profile amongst various surgical procedure within each route of administration are related to various factors, such as vascularity of the site of administration (see figures below).

Figure 3

Figure 12: Mean Plasma Bupivacaine Concentration with 266 mg EXPAREL After a Field Block in Various Surgical Procedure

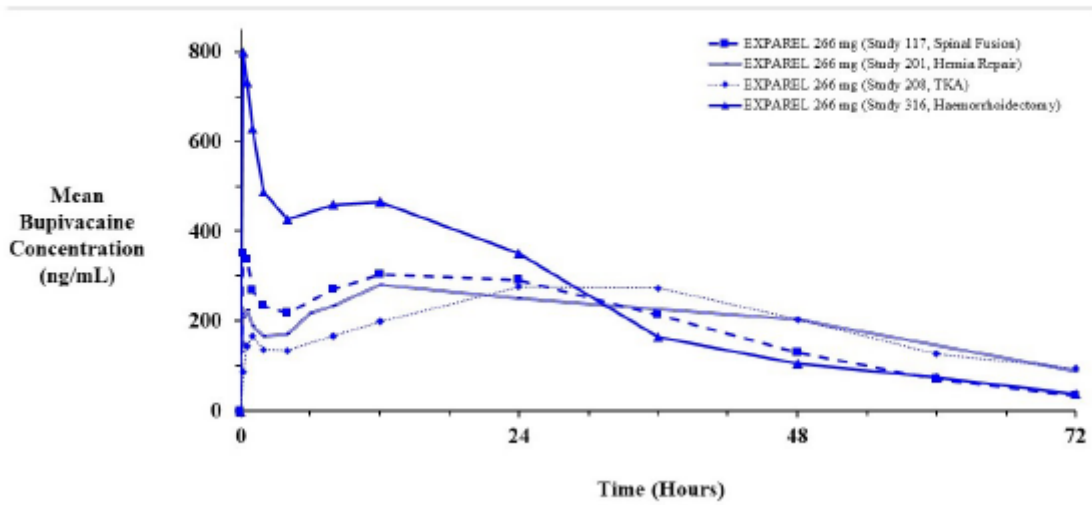


Figure 4

Figure 13: Mean Plasma Bupivacaine Concentration with 266 mg EXPAREL After a Peripheral Nerve Block in Various Surgical Procedure

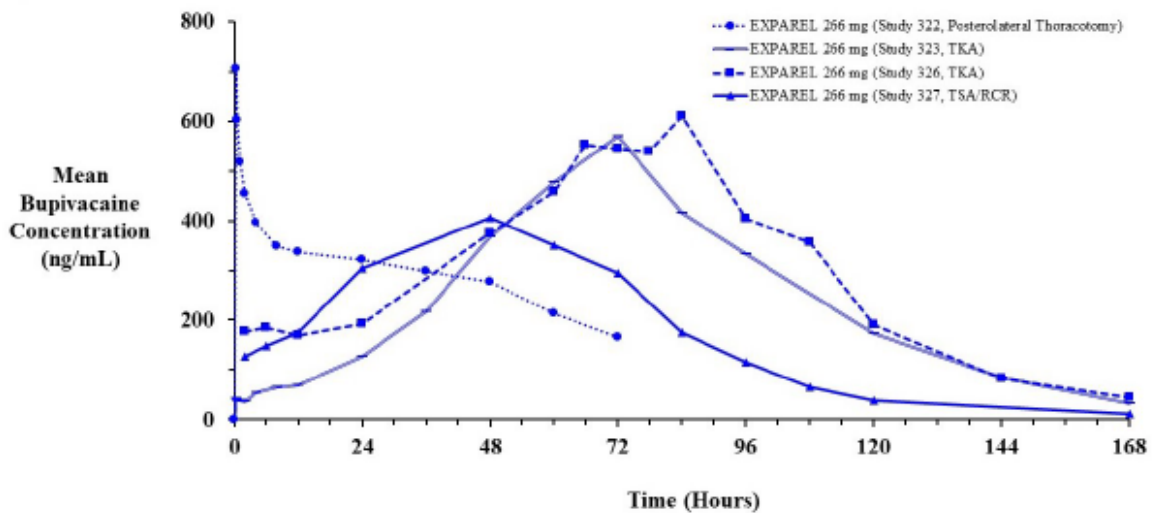
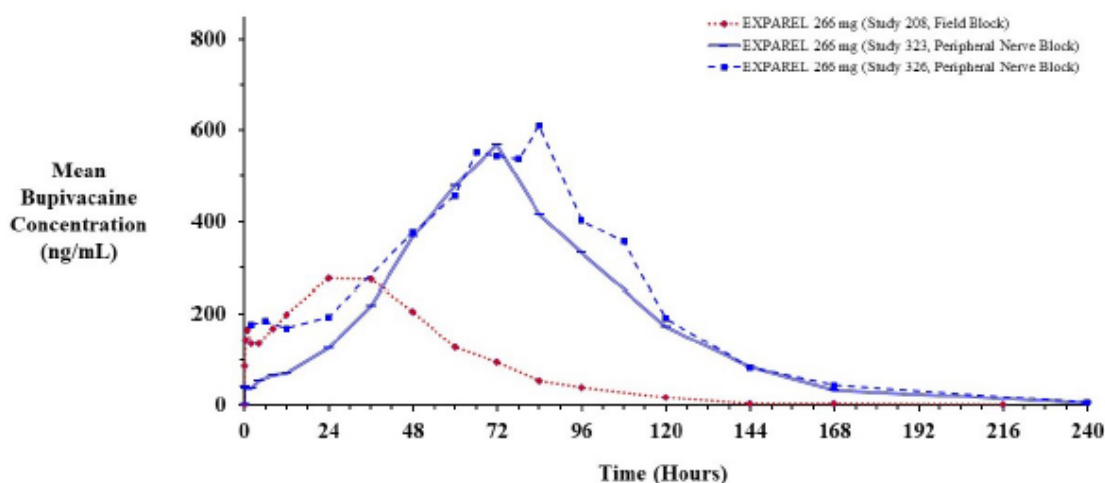


Figure 5

Figure 14: Mean Plasma Bupivacaine Concentration with 266 mg EXPAREL After a Filed Block or a Peripheral Nerve Block in Total Knee Arthroplasty



Overall, the PK studies demonstrated that administration of Exparel results in systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and for 120 hours after nerve block.

The rate of systemic absorption of bupivacaine is dependent upon the total dose of medicine administered, the route of administration, and the vascularity of the administration site.

Distribution

Once released from the multivesicular liposomes that comprise Exparel, bupivacaine distribution is expected to be the same as for any immediate release bupivacaine HCl formulation.

The applicant provided an extensive literature review and relied upon the product information from Marcaine.

Bupivacaine is distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

The rate and degree of diffusion is governed by the degree of plasma protein binding, the degree of ionisation, and the degree of lipid solubility.

Bupivacaine has a high protein binding capacity (95%) predominantly to α 1-acid glycoprotein and also albumin at higher concentrations. The plasma protein binding of bupivacaine is concentration-dependent. As the concentrations of free drug in plasma or serum increases, the percentage of drug that is bound to plasma proteins decreases until an equilibrium is reached between bound and unbound drug. A hepatic extraction ratio of 0.37 has been reported for bupivacaine in the literature after IV administration. A volume of distribution at steady state of 73l has been reported for bupivacaine.

Elimination

The applicant provided an extensive literature review and relied upon the product information from Marcaine.

- **Excretion**

Bupivacaine is extensively metabolised as evidenced by the minimal amount of parent drug in the urine.

- **Metabolism**

Metabolic clearance by the liver is the predominant route for plasma removal of bupivacaine.

Bupivacaine, like other amide-type local anaesthetics, is metabolised primarily in the liver via conjugation with glucuronic acid with approximately 5% converted to pipercolylxylidine (PPX). The primary liver enzyme in formation of PPX was shown to be CYP3A4 using liver microsomes, although CYP2C19 and CYP2D6 may play a minor role (Gantenbein et al, 2000).

The major metabolites detected in the urine after dosing with a rac-bupivacaine were, in the order of decreasing concentration, levo and dextro enantiomers of PPX, 4'-hydroxybupivacaine, and 3'-hydroxybupivacaine.

A large fraction of the hydroxylated metabolites of bupivacaine are excreted as glucuronide conjugates in the urine.

The lipid components of Exparel (ie, phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogues of endogenous lipids, and thus are metabolised like naturally occurring lipids.

- **Dose proportionality**

Dose proportionality was assessed from the PK data obtained in dose-escalation studies with different surgical procedures, including both local infiltration and peripheral nerve block administration (201, 208, 002, 203 and 323). Dose range investigated in those studies was 67 to 532 mg Exparel.

With Exparel single dose administration, bupivacaine C_{max} and AUC rose in an apparent dose proportional manner through all studies.

- **Time dependency**

Time-dependency was not formally assessed as Exparel is intended for single administration.

Intra- and inter-individual variability

Population PK analyses showed moderate to high interindividual variability (IIV) for the combined data of patients for the volume of distribution of the central compartment (V_c/F) (47.4% and 47.8%), and for the clearance (CL/F) (43.1% and 31.1%).

Very high between-subject variability in C_{max} and T_{max} was observed across field block and peripheral nerve block studies, 31.4% to 105.8% and 77% to 217.4%, respectively. High IIV for the absorption parameters was also confirmed in the nerve block population analysis.

No intra-individual variability was estimated since Exparel is intended for single administration.

Pharmacokinetics in target population

Pharmacokinetic analyses of individual studies provided useful information to understand the specific PK profile of Exparel in various surgical models. Additionally, two population PK models have been developed to characterise the PK of Exparel when administered as a field block and as a peripheral nerve block.

Special Populations**Special populations**

- **Impaired renal function**

The effect of renal impairment was investigated in the nerve block population PK analysis using EGFR as a covariate on CL/F. Renal function was measured in 3 studies (203, 326 and 327). No significant effect was identified. Categories of renal impairment were also evaluated graphically by diagnostic plots. No

effects of mild (n=201) and moderate (n=17) renal impairment were seen on the random effects on apparent clearance.

Consistent with expectations (since only 6% of bupivacaine is excreted unchanged in the urine), mild and moderate renal impairment did not influence the pharmacokinetics of bupivacaine. There was no data in patients with severe renal impairment.

Renal elimination plays only a minor role in excretion of bupivacaine. However, bupivacaine metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Impaired renal function should be considered when performing dose selection of Exparel.

- **Impaired hepatic function**

A dedicated hepatic impairment study was performed and hepatic function was assessed as a covariate in the population PK analysis.

Study 110 was conducted to study Exparel 266 mg via subcutaneous injection in a reduced study design comparing only moderate hepatic impairment group to age-, gender-, and weight-matched control subjects with normal hepatic function.

The results showed that exposure to total bupivacaine was approximately 50% higher in the moderate impairment group [GMR (90%CI) for C_{max} 1.48 (1.12, 1.96), AUC_{0-last} 1.72 (1.34, 2.20) and AUC_{0-∞} 1.73 (1.36, 2.22)]. The exposure to bupivacaine metabolite PPX increased approximately 2-fold [GMR (90% CI) for C_{max} 2.00 (1.19, 3.35), AUC_{0-last} 2.55 (1.46, 4.47) and AUC_{0-∞} 1.61 (1.01, 2.58)]. The mean (SD) total body clearance of bupivacaine was 16.95 (2.20) L/hour in subjects with moderate hepatic impairment compared with 31.21 (11.52) L/hour in subjects with normal hepatic function, a reduction of approximately 46%. The effect of moderate hepatic impairment on changes in protein binding was shown through unbound/total ratios for bupivacaine (1.8% vs 2.7%) and PPX (50.5% vs 64.8%) that were both higher for moderate impairment group compared to control group. The popPK model indicated the lack of effect of mild impairment on Exparel PK.

There was no data in patients with severe hepatic impairment.

No dose adjustment is recommended in patients with mild to moderate hepatic impairment. However, the product should be used cautiously in patients with hepatic disease as indicated in the proposed labelling.

- **Other intrinsic factors**

The effect of sex, race, weight and age was investigated in the population PK analysis (nerve block popPK model). Black race did not influence PK of bupivacaine. Age and sex influenced magnitude of the Late C_{max}, and body weight and BMI influenced values of the Early C_{max} according to the simulations. The magnitude of the observed differences was not considered clinically meaningful.

Interactions

No human drug interaction studies were performed. The applicant relied upon the published literature which was supplemented with several *in vitro* compatibility studies performed with Exparel, as well as two *in vivo* studies having Exparel admixed with immediate release bupivacaine HCl solution.

Using Exparel followed by other bupivacaine formulations has not been studied in clinical trials. The addition of local anaesthetics administered within 96 hours following administration of Exparel should take into account the total bupivacaine exposure.

Some physicochemical incompatibilities exist between Exparel and certain other drugs. Direct contact of Exparel with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering Exparel

characteristics and potentially affecting the safety and efficacy of Exparel. Therefore, admixing Exparel with other drugs prior to administration is not recommended.

The administration of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more.

Bupivacaine HCl administered together with Exparel may impact the PK and/or physicochemical properties of Exparel, and this effect is concentration dependent. Therefore, bupivacaine HCl and Exparel may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine HCl solution to Exparel does not exceed 1:2.

The toxic effects of these drugs are additive, and their administration should be used with caution including monitoring for neurologic and CV effects related to local anaesthetic systemic toxicity.

When a topical antiseptic such as povidone iodine is applied, the site should be allowed to dry before Exparel is administered into the site. Exparel should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Patients that are administered local anaesthetics may be at increased risk of developing methaemoglobinaemia when concurrently exposed to the oxidizing medicinal products.

Studies conducted with Exparel demonstrated that the most common implantable materials (polypropylene, polytetrafluoroethylene, silicone, stainless steel, and titanium) are not affected by the presence of Exparel any more than they are by saline. None of the materials studied had an adverse effect on Exparel.

Exposure relevant for safety evaluation

The most important PK consideration for a local anaesthetic is systemic toxicity. Systemic toxicity is associated with both the rate of rise in plasma concentration as well as the C_{max} level that is achieved. Bupivacaine levels that have been associated with CNS (>2000 ng/mL) and CV (>4000 ng/mL) toxicity have been previously reported (Tucker 1986; Knudsen 1997; Jorfeldt 1968; Bardsley 1998). In order to avoid systemic toxicity, the maximum recommended dose of bupivacaine HCl is 150-175 mg in single administration with a maximum total of 400 mg within a 24-hour period (e.g., by continuous infusion or repeat administration) (Marcaïn SmPC).

Comparative PK studies consistently demonstrated that systemic bupivacaine concentrations following Exparel administration were lower than equivalent doses of IR bupivacaine. Even in cases when the Exparel dose was higher than IR bupivacaine, the maximum bupivacaine concentrations observed with Exparel (i.e., highest outlying values) were 0.9- to 3.5-fold lower than IR bupivacaine with consistently lower mean C_{max} values reached at later times (i.e., T_{max}) due to the extended release of bupivacaine from Exparel.

The C_{max} above the safety threshold of 2000 ng/mL was reached in only one patient in the clinical development program, it was considered that this exemption is due to inadvertent intravascular administration.

Thus, clinicians should select the dose of Exparel that is appropriate for the analgesic need for a specific patient, as long as the selected dose is within the maximum recommended dose of 266 mg.

2.5.3. Pharmacodynamics

The pharmacology of bupivacaine has been extensively characterised in the scientific literature and it has been an approved local anaesthetic for several decades.

Mechanism of action

Local anaesthetics are used to achieve blockage of propagation of pain signals along nerve fibres by preventing the inward movement of sodium ions through the cell membranes of nerve fibres.

Local anaesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, but slowing the propagation of the nerve impulse, and by reducing the rate of rise in the action potential. The applicant states that the progression of anaesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibres. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Primary and secondary pharmacology

The primary efficacy endpoint for most of the Phase 3 studies was the cumulative pain intensity for a pre-specified duration as measured by the area under the curve (AUC).

The use of cumulative pain intensity scores as a primary efficacy endpoint was considered appropriate since the treatment goal with local anaesthetics is the prevention of moderate-to-severe pain.

Subjective pain assessments were collected using at least one of several validated measures: numeric rating scale at rest (NRS-R), numeric rating scale with activity (NRS-A), or visual analogue scale (VAS). (Note: not all measures were collected in every study.) For each endpoint, AUC was measured for a duration of effect appropriate to the surgical model under investigation.

Local anaesthetics provide their analgesic effects by depolarizing nerve fibres at the site of surgery or injury. However, the serum levels of local anaesthetics do assist in assessing the risk for the potential for systemic side effects such as central nervous system (CNS) or cardiovascular (CV) toxicity.

Integrated Cardiac Safety Report

Integrated Cardiac Safety Report was done by applicant to evaluate possible association between bupivacaine use and cardiovascular changes.

Integrated Summary of Safety (ISS) for cardiac safety and details the preclinical cardiac safety data followed by the definitive ICH E14 Thorough QT/QTc Study data that provide the most reliable method of determining the effect of Exparel on cardiac safety as defined by the changes observed in the electrocardiogram (ECG).

The applicant has included ECGs as part of the safety measurements employed to determine cardiac safety of Exparel in the seven clinical studies of the development program, corresponding clinical studies are summarised in Table 3.3.2 - 3

Table 7: Clinical studies Integrated Cardiac Safety Report

Study	Description
SKY0402-002	A Phase 1 study conducted in Edinburgh in 2004 in healthy volunteers which used dose escalation in 36 male subjects treated in four cohorts. No specific ECG data was obtained; ECG results of normal or abnormal were obtained predose, followed by continuing cardiac monitoring. All results from continuous monitoring after study drug administration were reported as normal for all subjects; no cardiac effects were commented upon.
SKY0402-021	A Phase 1 study conducted in Riccarton, Scotland in 2001 (entitled as study 019) in healthy volunteers using 10 and 50 mg SC injection of SKY0402 versus bupivacaine and placebo in nine male subjects in two stages. A screening 12-lead ECG was obtained and then after the injection of study drug a 6-hour single lead ECG was obtained. The study report does not note any ECG findings or cardiac events.
SKY0402-C-103	A Phase 1, randomised, double-blind, dose-finding study to evaluate the safety, PK, and pharmacodynamic profiles of SKY0402 administered via a single epidural injection to healthy volunteers. The study was conducted in Australia in 2005-2006. The objective of this study was to evaluate the epidural administration of SKY0402 with regard to safety, PK profile, and pharmacodynamic effects (presence, depth, extent, and duration of motor and sensory block). The study attempted to determine the dose (or dose range) of SKY0402 that may be safely administered to achieve a clinically optimal combination of sensory and motor block.
SKY0402-C-110	An Open-Label, Phase 1 Study to Assess the Pharmacokinetics and Safety of SKY0402 in Subjects with Impaired Hepatic Function, was conducted in Poland in 2009.
SKY0402-C-201	A Phase 2 dose-escalation study evaluating the safety, efficacy, and pharmacokinetics of SKY0402 administered by local infiltration for postoperative pain management in subjects undergoing inguinal hernia repair.
SKY0402-C-203	A Phase 2, multicentre, randomised, double-blind, dose-escalating/de-escalating study to evaluate the safety, efficacy, and pharmacokinetics of SKY0402 administered as a nerve block in the management of postoperative pain in subjects undergoing bunionectomy. This study was conducted in 2005-2006 in 15 sites in Europe and Australia.
SKY0402-C-208	A multicentre, randomised, double-blind, parallel-group, active-control, dose-ranging study to evaluate the safety, efficacy, and comparative systemic bioavailability of a single administration of SKY0402 via local infiltration for prolonged postoperative analgesia in subjects undergoing total knee arthroplasty (TKA).

The applicant, in recognition of the incompletely characterised relationship of bupivacaine use and cardiac effects, has conducted a complete development programme which included an ICH E14 compliant ECG trial and a total of 21 clinical trials (including 16 subjects who, after local administration into the

surgical wound, reached a bupivacaine plasma C_{max} >1 mg/L). In this programme, no cardiac signal of any kind has been detected.

Thorough QT/QTc Studies

The effect of Exparel on ECG parameters has been evaluated in two QT studies (Study 105 and Study 107) in healthy volunteers at supra-therapeutic doses as well as with ECG monitoring in all Exparel clinical studies. Based on applicant conclusions these two studies found that therapeutic and supra-therapeutic doses of Exparel did not have a clinically meaningful impact on cardiac repolarisation. The effect of Exparel on electrocardiogram (ECG) parameters has been evaluated in these two thorough QT studies evaluating supra-therapeutic doses of Exparel (300 mg up to 750 mg) administered to healthy volunteers.

Study SKY0402-C-105 was a single centre, randomised, double-blind, placebo- and positive controlled, five-way, crossover study conducted in 49 healthy volunteers to evaluate the effects of two dose levels of SKY0402 (300 mg and 450 mg) on the corrected QT interval, which was extended in Study SKY0402-C-107 to evaluate an additional two higher doses (600 mg and 750 mg) in 16 of the same subjects to be certain that an adequate supra-therapeutic dose was studied. The 600 mg subcutaneous dose and especially the 750 mg subcutaneous doses of SKY0402 administered in Study SKY0402-C-107 were selected in order to approximate the plasma levels normally seen in postoperative patients, thus allowing an assessment of the effect of these plasma levels on QTc. The 750 mg dose required multiple injections, and the Independent Ethics Committee commented on the "enormous" volume; therefore, this was considered the highest volume feasible.

Secondary objectives in Study 105 were to compare the effects of both dose levels of Exparel (266 mg subcutaneous and 399 mg subcutaneous) to placebo at each assessment time point on uncorrected QT and on QTc to describe categorical QT/QTc interval data and qualitative and quantitative ECG variations from baseline, to describe and compare them number and rates of AEs under each treatment, and to compare moxifloxacin 400 mg (single dose) to placebo on the largest time-matched mean QTc variation from baseline.

Study 107 was conducted to evaluate the effect of a single doses of Exparel (532 mg and 665 mg, subcutaneous) to placebo on the largest time-matched mean QTc variation from baseline.

Subjects in Study 107 were required to have completed Study 105. The results of the QTc analysis from Study 105 showed that Exparel did not have an effect on cardiac repolarisation. The largest time-matched mean QT interval corrected for heart rate using individual correction (QTcI) difference between Exparel 399 mg and placebo was -2.45 ms with a 90% confidence interval between -3.92 and -0.97 ms therefore indicating no QTc prolonging effect.

The results of the QTc analysis from Study 107 showed that a single suprathreshold dose of Exparel does not have an effect on cardiac repolarisation. The categorical analyses have shown that no subjects on Exparel 665 mg or Exparel 532 mg had increases from baseline in QTcI which were >60 msec or absolute QTcI values >500 msec.

The applicant has concluded, that the findings of this study and a previous study (105) demonstrate that a single dose of Exparel at 266 mg, 399 mg, 532 mg, or 665 mg does not prolong the QTc interval.

Combined Pool

The percentage of subjects with a post-treatment ECG interpreted as clinically significant abnormal was 3.5% in the All Exparel group, 3.9% in the IR bupivacaine group, and 0% in the placebo group in the Combined Pool.

Table 8: Summary of ECG Findings by Time Point Combined Local and Regional Analgesia Pool

Descriptor	EXPAREL					All Doses (N=1645) n (%)	IR Bupivacaine (N=625) n (%)	Placebo (N=604) n (%)
	<133 mg (N=169) n (%)	133 mg (N=322) n (%)	>133 mg -<266 mg (N=99) n (%)	266 mg (N=764) n (%)	>266 mg (N=291) n (%)			
Interpretation								
Baseline Visit								
N	19	292	48	416	75	850	232	314
Normal	9 (47.4)	168 (57.5)	37 (77.1)	218 (52.4)	46 (61.3)	478 (56.2)	148 (63.8)	166 (52.9)
Abnormal, NCS	0	110 (37.7)	8 (16.7)	145 (34.9)	19 (25.3)	282 (33.2)	80 (34.5)	102 (32.5)
Abnormal, CS	0	2 (0.7)	3 (6.3)	8 (1.9)	10 (13.3)	23 (2.7)	4 (1.7)	0
Abnormal [1]	10 (52.6)	12 (4.1)	0	45 (10.8)	0	67 (7.9)	0	46 (14.6)
Day 1 – End of Study								
N	12	287	48	214	71	632	77	272
Normal	4 (33.3)	172 (59.9)	37 (77.1)	89 (41.6)	38 (53.5)	340 (53.8)	47 (61.0)	137 (50.4)
Abnormal, NCS	0	101 (35.2)	7 (14.6)	84 (39.3)	25 (35.2)	217 (34.3)	27 (35.1)	97 (35.7)
Abnormal, CS	0	3 (1.0)	4 (8.3)	7 (3.3)	8 (11.3)	22 (3.5)	3 (3.9)	0
Abnormal [1]	8 (66.7)	11 (3.8)	0	34 (15.9)	0	53 (8.4)	0	38 (14.0)

Study 323 collected normal or abnormal (no further interpretation regarding clinical significance); the percentage of subjects with a post-treatment ECG interpreted as abnormal was 32.7% in the All Exparel and placebo groups.

Additionally, the percentage of subjects with a normal ECG at baseline and an abnormal ECG post-treatment (either not clinically significant or PCS) was similar among the treatment groups and no relationship with Exparel dose was observed.

Electrocardiogram and Holter Results from Studies 322 and 323

Holter recordings were collected in Studies 322 and 323, and these recordings have undergone substantial additional review and analyses. The applicant has concluded that there were no clinically relevant imbalances between the active study drug (liposome bupivacaine) and placebo for heart rate range, supraventricular or ventricular arrhythmias or bradycardic arrhythmias including sinus pauses >3 sec; AV block, or mean low heart rate.

Pharmacodynamic interactions

Exparel should be used with caution in patients receiving other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g., certain anti-arrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive.

Relationship between plasma concentration and effect

Exparel provides a prolonged duration of systemic bupivacaine levels compared with IR bupivacaine when administered as either a field block or a peripheral nerve block, indicating that Exparel is serving as a source of locally released bupivacaine over an extended time period.

The time period associated with systemic bupivacaine release from Exparel generally correlates with the prolonged duration of analgesic effect as illustrated by reductions in both pain intensity scores and use of opioid rescue medications for up to 72 hours.

The bupivacaine maximum plasma concentrations (Cmax) observed following administration of Exparel are lower than equivalent or even higher doses of IR bupivacaine, which may provide an enhanced safety margin against systemic toxicity.

Bupivacaine as local anaesthetic impart its analgesic effects by depolarizing nerve fibres at the site of surgery or injury. The plasma levels of local anaesthetics are not associated with primary pharmacologic

effect but are related to the risk for the potential systemic side effects such as central nervous system (CNS) or cardiovascular (CV) toxicity.

2.5.4. Discussion on clinical pharmacology

Pharmacokinetics

Population PK analyses

Two population PK analyses (one in field block and the other in peripheral nerve block setting) were conducted.

The population PK report provided for the field block setting was not sufficiently detailed to allow full assessment of the model in its objective of predicting PK in this setting. A full pop PK report was provided in the responses.

Standard methodology was used for model development and model evaluation. Based on the parameter estimates precision, diagnostic plots and visual predictive checks, the final models adequately described Exparel PK in field block and nerve block administration.

Several other concerns raised regarding presentation of pcVPCs, development of the covariate model, impact of shrinkage and simulations performed in the nerve block pop PK model were adequately resolved.

The purpose of popPK models was to predict bupivacaine PK for a variety of surgical procedures where Exparel is administered as a field block or nerve block, to estimate inter-individual variability and covariate effects. The model is used for informing the SmPC content on special populations. Overall, the models are considered to be of low regulatory impact.

Absorption

Across the comparative PK studies, half-life of bupivacaine in Exparel dose groups was longer than that of bupivacaine HCl. This is expected for extended-release formulations such as liposomal systems.

In several studies Exparel exhibited two concentration peaks: an early peak (associated with extra-liposomal bupivacaine) and a late plasma concentration peak (associated with release of the liposome-encapsulated bupivacaine). These were mainly local anaesthesia studies: posterior spinal fusion (Study 117), inguinal hernia (Study 201), total knee arthroplasty (Study 208), haemorrhoidectomy (Study 316), bunionectomy (Study 317), and regional ankle block for bunionectomy (Study 203).

Early T_{max} ranged from 0.3 – 1.36 hr while late C_{max} occurred from 13.6 – 45.3 hr in those studies. Early and late C_{max} values were higher at the administration sites of higher vascularity, consistent with the published literature. The highest values of both early and late C_{max} were in haemorrhoidectomy (Study 316; early 722.2 ng/mL, late 454.1 ng/mL).

Regional analgesia studies exhibited only a late concentration peak with detectable systemic plasma concentrations for a longer period compared to local analgesia.

SmPC was updated to reflect absorption of bupivacaine from Exparel in different surgical models.

Distribution

The SmPC information regarding distribution provided by the applicant relies extensively on the product information of the approved bupivacaine HCl product. It can be agreed with the that with regards to long history of bupivacaine use, information concerning distribution of liposomal bupivacaine can be generally based on published literature. The SmPC presents relevant data on bupivacaine distribution, as well as Exparel-specific information.

No human studies were performed to investigate disposition of lipid components of Exparel (dierucoylphosphatidyl-choline (DEPC), dipalmitoylphosphatidyl-glycerol, cholesterol and tricaprilyn). According to the applicant, they are naturally occurring or are close analogues of endogenous lipids and are expected to be metabolised like naturally occurring lipids. DEPC is a novel excipient that has not been previously used in other medicinal products authorised in the EU. It is a major constituent of the lipid bilayer membrane responsible for the prolonged-release characteristics of the product. The distribution of radiolabelled DEPC was evaluated in a study by quantitative whole-body autoradiography in rats. Please see Non-clinical discussion for further information.

Elimination

The SmPC information regarding elimination provided by the applicant relies extensively on the product information of the approved bupivacaine HCl product. It can be agreed with the applicant that with regards to long history of bupivacaine use, information concerning elimination of liposomal bupivacaine can be generally based on published literature. The SmPC was revised with more relevant data on bupivacaine elimination, as well as available Exparel-specific information.

According to the published literature, known metabolic pathways include N-dealkylation to PPX and hydroxylation to 4'-hydroxybupivacaine and 3'-hydroxybupivacaine. PPX seems to be the major metabolite of bupivacaine with less pharmacological activity. Metabolites are further conjugated with glucuronic acid and excreted by the kidney.

Two-fold lower clearance values were obtained in the population PK model after nerve block (10.6 L/h) compared to a field block (22.9 L/h). The observed differences in CL/F are likely explained by the Exparel exhibiting flip-flop kinetics, when absorption rate is slower than the elimination rate and becomes the rate limiting step. This further indicates that terminal slope characterises the absorption process and not the elimination.

Redosing

Data on redosing are available only from a single Phase 1 study (Study 113) in healthy volunteers where Exparel was administered subcutaneously. Even though plasma levels of bupivacaine following redosing did not appear concerning for administration in healthy volunteers, there are no data on such clinical use in patients undergoing surgical procedure. There is no evidence that the patient would benefit from the administration of the second dose, no data on how the need for a second dose would be judged by the clinician nor when would be the appropriate time for its administration. Moreover, there is no safety data presented from the robust post-marketing setting that would support administration of the second dose. Therefore, Exparel is recommended for single-dose administration only.

It is not known whether accumulation of DEPC could occur with redosing of Exparel. QBWA study in rats showed that DEPC can remain in the body even after 28 days. The applicant presumes the reason is its slow release from the liposomes. Once released from the liposomes, it is presumed that it would be rapidly cleared by the catabolism as the naturally occurring lipids. It is not considered likely that safety concerns would arise from accumulation.

Special populations

Renal impairment

No dedicated renal impairment study was conducted, therefore, no specific dose recommendations for patients with renal impairment can be made. Product information warns about the risk of systemic toxicity and requires caution when Exparel is administered in patients with renal impairment. This is supported. Additionally, results of the PopPK analysis for no effect of mild and moderate renal impairment have been added to section 5.2.

Hepatic impairment

The popPK model indicated the lack of effect of mild hepatic impairment on Exparel PK.

A dedicated study was performed in subjects with moderate hepatic impairment. As a worst-case scenario, the applicant presented estimated values and 90% confidence intervals for moderate hepatic impairment in surgical procedures with highest observed exposures (haemorrhoidectomy and intercostal nerve block). The exposure at the upper bound of 90%CI was below the safety threshold of 2000 ng/mL and even below 1500 ng/mL. It was considered highly unlikely that at total of 1500 ng/ml, the amount of unbound bupivacaine concentration for a moderately hepatically impaired patient could reach the toxicity threshold.

In the graphical analysis submitted by the applicant, no clear correlation was found between measures of bupivacaine exposure (C_{max} and AUC) and measures of hepatic function (albumin and total bilirubin).

The active substance in Exparel is a racemic bupivacaine. Even though bupivacaine is administered as a racemate (mixture of equal concentrations of R- and S-enantiomer), the two enantiomers have different pharmacological properties. No enantiomeric analysis was performed in the hepatic impairment study. Instead, a justification was given using published literature showing that similar (R):(S) enantiomer ratio can be expected in healthy subjects and subjects with hepatic impairment.

Subjects with severe hepatic impairment were not studied. Given the results of the moderate hepatic impairment and since hepatic metabolism is the primary route of bupivacaine elimination, significant effect on the bupivacaine exposure may be expected.

SmPC proposes no dose adjustment in patients with mild or moderate hepatic impairment. There are insufficient data to recommend the use of Exparel in patients with severe hepatic impairment. A warning follows that patients with hepatic disease may be more susceptible to potential toxicities of the amide-type local anaesthetics and that increased monitoring for LAST should be considered in subjects with moderate to severe hepatic disease.

Other intrinsic factors

In population pharmacokinetic models based on nerve block and wound infiltration clinical studies, approximately 29% decrease in clearance was observed in elderly patients which was not considered clinically relevant.

Interactions

No DDI studies were performed. Limited information is available in the literature regarding bupivacaine potential to cause DDIs as well as the potential to be a victim of a DDI both via metabolic enzymes and transporters. A literature reference (Palkama, 1999) which describes the extent of interaction when a strong CYP3A4 inhibitor (itraconazole) was administered with bupivacaine, leading to approximately 20-25% reduced bupivacaine clearance indicates that CYP3A4 may not be a major metabolic pathway. Since kidney is the main excretory organ for bupivacaine metabolites, it is possible that some transporters could be involved. Overall, due to very limited information, potential for interaction cannot be excluded. However, considering that Exparel is intended for single administration and there is a long history of bupivacaine use, it is acceptable that SmPC relies on the product information of the approved bupivacaine HCl product, as well as relevant Exparel-specific information.

Information on use with other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, because of additive systemic toxic effects has been added in the SmPC.

A major issue was initially raised regarding admixing Exparel with bupivacaine HCl. In studies 331 (TKA) and 411 (caesarean section), where 266 mg Exparel was administered admixed with bupivacaine HCl

(89 mg and 44 mg bupivacaine base, respectively), there were no PK measurements to evaluate bupivacaine C_{max} in such administration.

Two new clinical studies were submitted where PK and safety of admixing Exparel with bupivacaine HCl were evaluated:

- Study 122 (a phase 1, pilot, open label study to evaluate PK and safety of Exparel administered as sciatic nerve block (in popliteal fossa) for postsurgical analgesia in subjects undergoing bunionectomy) – in regional analgesia
- Study 123 (a phase 1, pilot, open label study to evaluate PK and safety of Exparel administered as pectoral plane block in women undergoing breast augmentation surgery) – in local analgesia

The SmPC allows admixing Exparel and bupivacaine HCl (immediate release formulation) in the same syringe if considered needed, as long as the ratio of the milligram dose of bupivacaine solution to Exparel does not exceed 1:2. Since such admixing could in some cases potentially lead to exceeding the maximum daily dose of bupivacaine HCl (400 mg) and reaching the safety threshold for systemic bupivacaine plasma concentrations, an additional warning, as well as the formula to facilitate the calculation of the total bupivacaine HCl equivalents is stated. The total amount of bupivacaine HCl and Exparel being co-administered should not exceed 400 mg equivalents of bupivacaine HCl. Bupivacaine amount in Exparel is expressed as the free base of bupivacaine, thus, when calculating the total dose of bupivacaine for co-administration, the amount of bupivacaine from Exparel should be converted to the equivalent of bupivacaine HCl by multiplying Exparel dose with a factor of 1.128. Caution is advised when co-administering Exparel and bupivacaine HCl, particularly when administering to highly vascular areas where higher systemic absorption is expected.

2.5.5. Conclusions on clinical pharmacology

The applicant provided comprehensive PK data for different surgical models. High variability was observed in the absorption parameters between different surgical models. More rapid absorption and higher exposures are expected with administration in more vascular areas. Clinical pharmacology of Exparel is considered adequately characterised.

2.6. Clinical efficacy

2.6.1. Dose response study(ies)

Six Phase 2 studies (201, 203, 207, 208, 209, 210) have been done. Study 211 that was terminated early due to slow enrolment and no formal efficacy analysis was performed. No clear dose-response correlation is obvious from the presented studies with the exception of Study 209. However, Phase 2 results are of exploratory nature and the numbers analysed are small precluding any firm conclusions about efficacy to be made.

2.6.2. Main study(ies)

The applicant has completed 11 pivotal Phase 3, randomised, double blind, multicentre studies to evaluate the efficacy of Exparel. The efficacy was assessed in seven pivotal Phase 3 clinical studies as a field block to provide local analgesia and in four pivotal Phase 3 clinical studies as a peripheral nerve block to provide regional analgesia.

Two pivotal Phase 3 clinical studies (Study 331 and Study 411) evaluated Exparel admixed with IR bupivacaine. This was done because some clinicians admix Exparel with IR bupivacaine to control impact of nonpharmacologic factors (such as the dose, location, vascularity of the site of administration, and variance in surgical technique) on the time to onset of effective analgesia.

The pivotal Phase 3 studies in local analgesia and regional analgesia are summarised in section 2.5.1 of this report.

Methods

Study Participants

The pivotal Phase 3 studies enrolled subjects who were undergoing various surgeries associated with moderate-to-severe pain. The applicant claims that study populations represent a typical cross-section of adult patients aged 18 years or older who experience post-surgical pain for the respective study procedures. Age ranged from 18 to 89 years.

The key inclusion criteria across the studies were similar, with minor differences taking into account particular surgery.

Key Inclusion criteria:

- male or female, ≥ 18 years of age,
- American Society of Anesthesiologists (ASA) physical status 1, 2, 3 or 4 (in particular studies)
- Were scheduled to undergo surgical procedure of interest (as per study protocol)

Key exclusion criteria were similar across the studies with minor differences according to the particular surgical procedure

Key exclusion criteria:

- Use of any of the following medications within the times specified before surgery: long-acting opioid medication or NSAIDs (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication within 24 hours
- Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) were being given to control pain: selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject was taking one of these medications for a reason other than pain control, he/she must have been on a stable dose for at least 1 month prior to study drug administration.
- Current use of systemic glucocorticosteroids within 1 month of enrolment in the study.
- Severely impaired renal or hepatic function (e.g., serum creatinine level >2 mg/dL [176.8 $\mu\text{mol/L}$], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase level >3 times the upper limit of normal, or serum alanine aminotransferase level >3 times the upper limit of normal)
- Any neurologic or psychiatric disorder that might have impacted postsurgical pain or interfered with study assessments
- Malignancy in the last 2 years, according to physician discretion
- Rheumatoid or inflammatory arthritis or disease that required chronic analgesic treatment
- Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever was longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study

Treatments

In all studies except Study 326 patients were randomised into 2 treatment groups. However, in the Study 326 later enrolment in the second Exparel dosing group was stopped due to new published data on efficacy of a particular dose. Either placebo or IR bupivacaine was used as a comparator in all clinical studies. The comparators used in the efficacy studies are in compliance with the current guidelines, and IR bupivacaine is considered as a standard of care, thus acceptable as an active control. Exparel doses in SmPC are in line with the doses studied.

In a local analgesia studies a single dose of study drug was administered intraoperatively via field block on Day 1.

In a regional analgesia studies a study drug was administered via nerve block 1-2 hours prior surgery or after the posterolateral thoracotomy (in study 322).

Rescue medication

In all studies, rescue pain medication was available for subjects for whom study medication did not provide adequate pain relief. When study drug medication was perceived to be inadequate, subjects had the option to receive a pre-specified regimen of rescue pain medication. The choice of the drug, dose, and sequence (i.e., first-line, second-line, etc.) for each study was selected based on what was thought to be most appropriate for the surgical model and clinical situation. The types of rescue pain medication used in the clinical development programme included oral acetaminophen/paracetamol, opioid analgesics (oral, intramuscular [IM], or intravenous [IV] or via PC pump), and IR local anaesthetics. For all studies, opioid consumption is reported as the morphine equivalent dose.

The rescue medication varied across studies due to differences in the pain models (surgical procedures) studied. The use of opioid and non-opioid rescue medications is considered acceptable.

Objectives

The primary objective in local and regional analgesia studies was to demonstrate superiority of Exparel vs comparator, to evaluate the magnitude and duration of the effect of a single intraoperative administration or single-dose injection block of Exparel vs comparator, to demonstrate the analgesic efficacy of single-dose local administration of Exparel compared with placebo, or to compare pain control and total opioid consumption following local infiltration analgesia with Exparel.

Outcomes/endpoints

The primary efficacy endpoints for most of the Phase 3 studies were the cumulative pain intensity for a pre-specified duration as measured by the area under the curve (AUC). For each endpoint, AUC was measured for a duration of effect appropriate to the surgical model under investigation.

The applicant claimed that use of cumulative pain intensity scores over an extended duration as a primary efficacy endpoint was considered appropriate since the treatment goal with local anaesthetics is the prevention of moderate-to-severe pain. The treatment paradigm for local anaesthetics contrasts with studies of other analgesics (e.g., opioids) whose efficacy is measured based on reductions in pain intensity from baseline, which is typically assessed by the sum of pain intensity differences.

Each of the Phase 3 studies assessed postsurgical opioid consumption-related endpoints. The key secondary efficacy endpoints in the Exparel clinical development programme included:

- total consumption of postsurgical opioids
- percentage of opioid-free subjects
- time to first use of opioid rescue medication

Additional secondary endpoints were collected, as appropriate, to assess the secondary objectives of each study. Other secondary endpoints evaluated during clinical development included:

- sensory and motor function assessments
- overall benefit of analgesia score (OBAS), a multidimensional instrument that assesses
- pain, satisfaction, and symptoms
- subject satisfaction with overall analgesia
- discharge readiness using the Modified Postanesthesia Discharge Scoring System

Randomisation and blinding (masking)

In pivotal phase 3 local analgesia studies patients were randomised at the ratio 1:1, except Study 329, where Exparel was used in patients undergoing third molar extraction and randomisation ratio was 2:1.

In pivotal phase 3 regional analgesia studies patients were randomised at the ratio 1:1, except Study 326 where subjects were randomised at the ratio 1:1:1.

The randomisation code was generated by a centralised randomisation system, which was also used to communicate subject randomisations to the study sites. All randomised subjects had both a unique subject identifier and a unique random code identifier. No subject or random code identifiers were reused once assigned.

In the relevant studies the randomisation was stratified by site and modality of anaesthesia.

Exparel and placebo are visually distinguishable; therefore, to maintain the double-blind study design, only unblinded study personnel who were NOT involved with protocol-specific, postsurgical assessments prepared the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects remained blinded to the assigned treatment throughout the study. If a subject experienced a serious AE (SAE), the applicant did not automatically unblind the subject's treatment, unless it was necessary to manage treatment of the SAE.

The applicant noted, that site surveys suggested that study sites would vary in their standard (and feasible) procedures for preparing sterile study drug in a blinded fashion. Therefore, each site was responsible for providing their written blinding procedures for study drug preparation and transportation. This documentation (eg, site-specific blinding plan) was made available to the applicant for review before the site enrolled a subject into the study. The site-specific blinding plan outlined the study treatment blinding process that was to be followed at the site throughout the study.

Statistical methods

The statistical methods used were similar across the studies with differences related to endpoints, sample size and such study characteristics as sites (only US or US and Europe).

Descriptive summaries were provided where appropriate for each of the primary and secondary efficacy and safety endpoints.

Efficacy data were summarised by treatment group. Exparel was compared with placebo or IR bupivacaine using analysis of variance (ANOVA) or covariance (ANCOVA) with treatment and site (where appropriate) as the main effect for the primary efficacy endpoint.

For comparisons of Exparel to placebo for the secondary efficacy endpoints the analysis of variance (ANOVA), Cochran-Mantel-Haenszel tests and log-rank tests for continuous and categorical endpoints where appropriate were used.

In all studies except for Study 311 and 312, pain intensity scores were imputed for use of rescue pain medication using the worst windowed observation carried forward method. The worst windowed observation carried forward method imputed pre-rescue pain intensity scores for the half-life of the respective rescue medication.

For the analysis of secondary efficacy endpoints in some studies a hierarchical, fixed-sequence stepwise testing procedure was used. If the first test was significant at the 0.05 level, only then, the next secondary efficacy measure was tested, and so forth. The results were declared statistically significant at the 0.05 significance level.

In some studies, there were several amendments to the initial SAP. The major amendment and post-hoc analysis were performed in Study 329. In general SAPs are considered acceptable and statistical analysis methods used, including handling of missing data and use of rescue medication are considered adequate.

Results

Participant flow

The participants flow is presented for each study.

Phase 3 Studies in Local Analgesia (311, 312, 316, 317,329, 331, and 411)

Study 311

A summary of the subject disposition and analysis populations is presented in Table 9.

Table 9: Subject Disposition and Analysis Populations in Study 311

	EXPAREL 532 mg	IR Bupivacaine 177 mg
Subjects Randomised, N	122	129
Not Dosed	1	5
Dosed	121	124
Safety Subset, n (%)	122 (100)	123 (95.3)
Full Analysis Set, n (%)	108 (88.5)	110 (85.3)
Subjects Who Completed the Study, n (%)	116 (95.9)	114 (91.9)
Subjects Who Terminated Early, n (%)	5 (4.1)	10 (8.1)
Reason for Early Termination, n (%)		
Adverse Event	0	2 (1.6)
Lost to Follow-up	1 (0.8)	2 (1.6)
Consent Withdrawn	3 (2.5)	4 (3.2)
Other	1 (0.8)	2 (1.6)

IR=immediate-release

Source: [Study 311 CSR, Table 14.1.1.1](#) and [Table 14.1.1.2](#)

Study 312

A summary of the subject disposition and analysis populations is presented in Table 10.

Table 10: Subject Disposition and Analysis Populations in Study 312

	EXPAREL 266 mg	IR Bupivacaine 89 mg
Subjects Randomised, N	109	111
Not Dosed	8	8
Dosed	101	103
Safety Subset, n (%)	101 (92.7)	103 (92.8)
Full Analysis Set, n (%)	99 (90.8)	99 (89.2)
Subjects Who Completed the Study, n (%)	101 (100.0)	97 (94.2)
Subjects Who Terminated Early, n (%)	0	6 (5.8)
Reason for Early Termination, n (%)		
Lost to Follow-up	0	6 (5.8)

IR=immediate-release

Source: [Study 312 CSR, Tables 14.1.1.1 and 14.1.1.2](#)

Study 316

A summary of the subject disposition and analysis populations is presented in Table 11.

Table 11: Subject Disposition and Analysis Populations in Study 316

	EXPAREL 266 mg	Placebo
Subjects Randomised, N	96	94
Not Dosed	1	0
Dosed	95	94
Safety Population, n (%)	95	94
Full Analysis Set, n (%)	94 (98.9)	93 (98.9)
Subjects Who Completed the Study, n (%)	94 (98.9)	92 (97.9)
Subjects Who Terminated Early, n (%)	1 (1.1)	2 (2.1)
Per Protocol Population, n (%)	92 (96.8)	92 (97.9)
Reason for Early Termination, n (%)		
Consent Withdrawn	1 (1.1)	2 (2.1)

Source: [Study 316 CSR, Table 14.1-1](#)

Study 317

A summary of the subject disposition and analysis populations is presented in Table 12.

Table 12: Subject Disposition and Analysis Populations in Study 317

	EXPAREL 106 mg	Placebo
Subjects Randomised, N	98	97
Not Treated	1	1
Treated	97	96
Safety Population, n (%)	97 (100.0)	96 (100.0)
Full Analysis Set, n (%)	97 (100.0)	96 (100.0)
Per Protocol Population, n (%)	93 (95.9)	94 (97.9)
Subjects who Completed Study, n (%)	93 (95.9)	92 (95.8)
Subjects who Terminated Early, n (%)	4 (4.1)	4 (4.2)
Reason for Early Termination, n (%)		
Adverse Event	0	1 (1.0)
Subject Withdrew Consent	1 (1.0)	3 (3.1)
Other	3 (3.1)	0

Source: Study 317 CSR, Table 14.1-1

Study 329

The summary of patient disposition in this study is presented in Table 13.

Table 13: Summary of subject disposition (all screened subjects)

	EXPAREL (N=107) n (%)	Placebo (N=59) n (%)	Total (N=166) n (%)
Screened ¹			275
Randomized	107	59	166
Not treated	2	2	4
Treated	105	57	162
Safety analysis set ²	105 (98.1)	57 (96.6)	162 (97.6)
Per-protocol efficacy analysis set ³	59 (55.1)	30 (50.8)	89 (53.6)
Primary efficacy analysis set ³	99 (92.5)	51 (86.4)	150 (90.4)
Secondary efficacy analysis set ³	105 (98.1)	57 (96.6)	162 (97.6)
PK analysis set ⁴	105 (98.1)	NA	105 (63.3)
Completed study	97 (90.7)	57 (96.6)	154 (92.8)
Discontinued from the study	10 (9.3)	2 (3.4)	12 (7.2)
Reasons for discontinuation	10 (9.3)	2 (3.4)	12 (7.2)
Death	0	0	0
Adverse event	0	0	0
Lack of efficacy	0	0	0
Lost to follow-up	4 (3.7)	0	4 (2.4)
Withdrawal by subject	4 (3.7)	0	4 (2.4)
Other	2 (1.9)	2 (3.4)	4 (2.4)

NA = not applicable.

Number of subjects randomized is used as the denominator for calculation of PK parameters. All subjects were treated as randomized.

- 1: All subjects who signed the informed consent form.
- 2: All subjects who received study drug.
- 3: Subjects who received study drug and underwent surgery.
- 4: Subjects who received EXPAREL.

Study 331

A summary of the subject disposition and analysis populations is presented in Table 14.

Table 14: Subject Disposition and Analysis Populations in Study 331

	EXPAREL 266 mg + IR Bupivacaine 89 mg	IR Bupivacaine 89 mg
Randomised, N	71	69
Not treated	1	0
Treated	70	69
Safety Analysis Set, n (%)	70 (98.6)	69 (100)
Efficacy Analysis Set, n (%)	70 (98.6)	69 (100)
Per-protocol Analysis Set, n (%)	53 (74.6)	56 (81.2)
Completed study, n (%)	68 (95.8)	67 (97.1)
Discontinued from the study, n (%)	3 (4.2)	2 (2.9)
Reasons for discontinuation, n (%)		
Withdrawal by subject	2 (2.8)	1 (1.4)
Other	1 (1.4)	1 (1.4)

IR: immediate-release

Source: [Study 331 CSR, Table 14.1-1.1](#)

Study 411

A summary of the subject disposition and analysis populations is presented in Table 15.

Table 15: Subject Disposition and Analysis Populations in Study 411

	EXPAREL 266 mg + IR Bupivacaine 44 mg	IR Bupivacaine 44 mg
Randomised, N	96	90
Not treated	0	0
Treated	96	90
Safety Analysis Set, n (%) ^a	97 (101.0)	89 (98.9)
Efficacy Analysis Set, n (%) ^b	71 (74.0)	65 (72.2)
Completed Study, n (%)	91 (94.8)	83 (92.2)
Discontinued from the study, n (%)	5 (5.2)	7 (7.8)
Reasons for discontinuation, n (%)		
Lost to follow up	5 (5.2)	7 (7.8)

^a Includes one subject that was randomised to the IR bupivacaine group but was treated with EXPAREL 266 mg.

^b Efficacy analysis set includes all subjects who underwent caesarean section and met the study criteria for correct transversus abdominis plane placement, local anaesthetic dosing, and multimodal post-operative analgesic regimen.

IR: immediate-release

Source: [Study 411 CSR, Table 14.1.1](#)

Phase 3 Studies in Regional Analgesia (322, 323 Part 2, 326, 327)

Study 322

A summary of the subject disposition and analysis populations is presented in Table 16.

Table 16: Subject Disposition and Analysis Populations in Study 322

	EXPAREL 266 mg	Placebo
Subjects Randomised, N	96	95
Not Treated	2	4
Treated	94	91
Safety Analysis Set, n (%)	94 (97.9)	91 (95.8)
Efficacy Analysis Set, n (%)	94 (97.9)	91 (95.8)
Subjects who Completed Study, n (%)	82 (85.4)	74 (77.9)
Subjects who Terminated Early, n (%)	14 (14.6)	21 (22.1)
Reason for Early Termination, n (%)		
Subject Death	2 (2.1)	1 (1.1)
Adverse Event	2 (2.1)	7 (7.4)
Lack of Efficacy	8 (8.3)	10 (10.5)
Withdrawal by Subject	0	2 (2.1)
Other	2 (2.1)	1 (1.1)

Source: [Study 322 CSR, Table 14.1.1.1](#)

Study 323 (part 2)

A summary of the subject disposition and analysis populations is presented in Table 17.

Table 17: Subject Disposition and Analysis Populations in Study 323 (Part 2)

	EXPAREL 266 mg	Placebo
Subjects Randomised, N	99	97
Not Treated	7	6
Treated	92	92
Safety Analysis Set, n (%)	92 (92.9)	92 (94.8)
Efficacy Analysis Set, n (%)	92 (92.9)	91 (93.8)
Subjects who Completed Study, n (%)	82 (82.8)	82 (84.5)
Subjects who Terminated Early, n (%)	17 (17.2)	15 (15.5)
Reason for Early Termination, n (%)		
Lack of Efficacy	2 (2.0)	2 (2.1)
Lost to Follow-up	2 (2.0)	0
Withdrawal by Subject	3 (3.0)	3 (3.1)
Other	10 (10.1)	10 (10.3)

Source: [Study 323 CSR, Table 14.1.1-2](#)

Study 326

A summary of the subject disposition and analysis populations is presented in Table 18.

Table 18: Subject Disposition and Analysis Populations in Study 326

	EXPAREL		Placebo
	133 mg	266 mg	
Randomised, N	76	77	79
Not Treated	1	1	0
Treated	75	76	79
Efficacy Analysis Set, n (%)	75 (98.7)	76 (98.7)	79 (100)
Completed Study, n (%)	75 (98.7)	73 (94.8)	74 (93.7)
Discontinued from Study, n (%)	1 (1.3)	4 (5.2)	5 (6.3)
Adverse Event	0	1 (1.3)	1 (1.3)
Withdrawal by Subject	0	3 (3.9)	4 (5.1)
Other	1 (1.3)	0	0

Source: Study 326 CSR, Table 14.1-1

Study 327

A summary of the subject disposition and analysis populations is presented in Table 19.

Table 19: Subject Disposition and Analysis Populations in Study 327

	EXPAREL		Placebo
	133 mg	266 mg	
Randomised, N	69	15	72
Not Treated	0	0	1
Treated	69	15	71
Efficacy Analysis Set, n (%)	69 (100)	15 (100)	71 (98.6)
Completed Study, n (%)	68 (98.6)	15 (100)	71 (98.6)
Discontinued from Study, n (%)	1 (1.4)	0	0
Reasons for Discontinuation, n (%)			
Other	1 (1.4)	0	0

Source: Study 327 CSR, Table 14.1-1

Study 327 initially evaluated both 133-mg and 266-mg doses of Exparel. Shortly after enrolment in the study was initiated, newly published data from an investigator-initiated trial became available suggesting that the 133-mg dose of Exparel provided adequate magnitude and duration of analgesic effect (Vandepitte et al 2017), so an administration decision was made to discontinue enrolment in the 266 mg group.

All studies in the clinical development programme were conducted on an inpatient basis, so study completion rates were generally high.

Overall, the discontinuation rates were low. Only in regional analgesia studies (Study 322 and 323) the reason for discontinuation was lack of efficacy. The discontinuation rates due to adverse effect was low across all studies and the rates were lower in Exparel group.

Baseline data

The study population in all Phase 3 studies reflects common standard population in terms of surgical procedures and age distribution/mean age. Although there are differences in the baseline characteristics and demographics across studies, the comparison groups in each study were overall well balanced.

Numbers analysed

The primary efficacy analysis population (i.e., Full Analysis Set [FAS] or Efficacy Analysis Set [EAS]) for each respective study is comprised of subjects who received study drug, underwent the planned surgical procedure, and for whom AUC of pain intensity scores could be calculated.

Outcomes and estimation

Phase 3 Studies in Local Analgesia (311, 312, 316, 317, 329, 331, and 411)

Seven pivotal Phase 3 studies evaluated Exparel as a field block to provide local analgesia at a range of doses from 106 mg to 532 mg in TKA, haemorrhoidectomy, bunionectomy, third molar extraction, and caesarean section. Four studies were active-controlled studies against IR bupivacaine and three studies were placebo-controlled. The primary efficacy endpoint results are summarised in Table 20.

Table 20: Primary Efficacy Endpoint Results in Pivotal Phase 3 Studies in Local Analgesia

Study	Surgery Type	EXPAREL Dose / Control	Primary Endpoint	Treatment Difference / Ratio (95% CI)	P-value
311	TKA	532 mg / IR Bupi 177 mg	AUC NRS-A ₀₋₇₂	23.0 (-6.6, 52.5)	0.13
312	Haemorrhoidectomy	266 mg / IR Bupi 89 mg	AUC NRS-R ₀₋₉₆	40.7 (-14.9, 96.3)	0.15
316	Haemorrhoidectomy	266 mg / Placebo	AUC NRS-R ₀₋₇₂	-60.7 (-90.4, -31.0)	<0.0001
317	Bunionectomy	106 mg / Placebo	AUC NRS-R ₀₋₂₄	-22.3 (-34.8, -9.8)	0.0005
329	Third molar extraction	133 mg / Placebo	AUC NRS-R ₀₋₄₈	-2.7 (-33.5, 28.2)	0.87
331	TKA	266 mg + IR Bupi 89 mg / IR Bupi 89 mg	AUC VAS ₁₂₋₄₈	-26.9 (-56.6, 2.8)	0.038
			Opioid consumption through 48 hours	0.203 (0.065, 0.631)	0.003
411	Caesarean section	266 mg + IR Bupi 44 mg / IR Bupi 44 mg	Opioid consumption through 72 hours	-16.5 (-30.8, -2.2)	0.012

AUC = area under the curve; CI = confidence interval; IR Bupi = immediate-release bupivacaine; NRS-A₀₋₇₂ = numerical rating scale with activity from 0 to 72 hours; NRS-R₀₋₂₄ = numerical rating scale at rest from 0 to 24 hours; NRS-R₀₋₄₈ = numerical rating scale at rest from 0 to 48 hours; NRS-R₀₋₇₂ = numerical rating scale at rest from 0 to 72 hours; NRS-R₀₋₉₆ = numerical rating scale at rest from 0 to 96 hours; TKA = total knee arthroplasty; VAS₁₂₋₄₈ = visual analogue scale from 12 hours to 48 hours

The summary of significant key opioid endpoint results is provided in Table 21.

Table 21: Summary of Key Opioid Endpoint Results in Positive Phase 3 Local Analgesia Studies

Study	Opioid Rescue Medication Use	Opioid-free / Opioid-spared	Time to First Opioid Rescue Medication Use
316	<ul style="list-style-type: none"> 45% reduction in geometric LS mean ratio through 72 hours (p=0.0006) 	<ul style="list-style-type: none"> 27.7% versus 9.7% opioid free through 72 hours (p=0.0007) 	<ul style="list-style-type: none"> Median 14.3 versus 1.2 hours (log-rank p<0.0001)
317	<ul style="list-style-type: none"> 19% reduction in the mean number of Percocet tablets used through 24 hours (p=0.0077) 	<ul style="list-style-type: none"> 7.2% versus 1.0% opioid free through 24 hours (p=0.040) 	<ul style="list-style-type: none"> Median 7.2 versus 4.3 hours (log-rank p<0.0001)
331	<ul style="list-style-type: none"> 80% reduction in geometric LS mean ratio through 48 hours (p=0.0029) 	<ul style="list-style-type: none"> 10% versus 0% opioid free through 48 hours (p=0.009) 	<ul style="list-style-type: none"> Median 4.1 versus 2.9 hours (log-rank p=0.023)
411	<ul style="list-style-type: none"> 52% reduction in LS mean through 72 hours (p=0.0117) 	<ul style="list-style-type: none"> 53.5% versus 24.7% opioid spared through 72 hours (p=0.0012) 51.9% versus 48.6% opioid free through 72 hours (p=0.3609) 	<ul style="list-style-type: none"> Median 53.2 versus 41.1 hours (log-rank p=0.75)

LS: least squares

Studies 316, 317, 331, and 411 in local analgesia met their respective primary efficacy endpoints. These studies demonstrated the analgesic efficacy of Exparel doses of 106 mg to 266 mg through 24 to 72 hours. The applicant concluded that, these studies showed that Exparel extends the maximum duration of analgesic effect that can be achieved with conventional IR bupivacaine when used to provide for local analgesia for the management of acute pain with a reduction in the need for opioid rescue pain medication.

Three pivotal Phase 3 studies in local analgesia (Studies 311, 312, and 329) did not achieve their respective primary efficacy endpoint. The applicant argue, that acute pain studies are known to be subject to a wide variety of study design, methodologic, and study conduct issues that can reduce the ability to detect a statistically significant effect of an efficacious medication.

Phase 3 Studies in Regional Analgesia (322, 323 Part 2, 326, 327)

Four pivotal, placebo-controlled Phase 3 studies evaluated Exparel as a peripheral nerve block to provide regional analgesia at either the 133 mg or 266 mg doses in posterolateral thoracotomy, TKA, or TSA/RCR. The primary efficacy endpoint results are summarised in Table 22.

Table 22: Primary Efficacy Endpoint Results in Pivotal Phase 3 Studies in Regional Analgesia

Study	Surgery Type	EXPAREL Dose / Control	Primary Endpoint	Treatment Difference / Ratio (95% CI)	P-value
322	Posterolateral thoracotomy	266 mg / Placebo	AUC NRS-R ₀₋₇₂	13.1 (-31, 57)	0.560
323 (Part 2) ^a	TKA	266 mg / Placebo	AUC NRS-R ₀₋₇₂	-96.5 (-144, -49)	<0.0001
326	TKA	133 mg / Placebo	AUC VAS ₀₋₇₂	-20.2 (-72.4, 31.9)	0.446
		266 mg / Placebo		-28.8 (-80.5, 22.9)	0.275
327	TSA/RCR	133 mg / Placebo	AUC VAS ₀₋₄₈	-117.7 (-150.9, -84.5)	<0.0001

AUC = area under the curve; CI = confidence interval; NRS-R₀₋₇₂ = numerical rating scale at rest from 0 to 72 hours; RCR = rotator cuff repair; TKA = total knee arthroplasty; TSA = total shoulder arthroplasty; VAS₀₋₄₈ = visual analogue scale from 0 to 48 hours; VAS₀₋₇₂ = visual analogue scale from 0 to 72 hours

^a Study 323 was a two-part Phase 2/Phase 3 study. Results from Phase 3 (Part 2) are summarised.

Source: [Module 2.7.3](#), [Table 36](#), [Table 40](#), [Table 44](#), [Table 48](#)

The summary of significant key opioid endpoint results is provided in Table 23.

Table 23: Summary of Key Opioid Endpoint Results in Positive Phase 3 Regional Analgesia Studies

Study	Opioid Rescue Medication Use	Opioid-free Subjects	Time to First Opioid Rescue Medication Use
323 ^a	<ul style="list-style-type: none"> 26% reduction in geometric LS mean ratio through 72 hours (p=0.0016) 	<ul style="list-style-type: none"> No subjects opioid free at 72 hours in either group 	<ul style="list-style-type: none"> Median 0.4 versus 0.4 hours (log-rank p=0.96)
327	<ul style="list-style-type: none"> 77% reduction in geometric LS mean ratio through 48 hours (p<0.0001) 	<ul style="list-style-type: none"> 13.0% versus 1.4% opioid free at 48 hours (p=0.008) 	<ul style="list-style-type: none"> Median 4.2 versus 0.6 hours (log-rank p<0.0001)

^a Study 323 was a combined Phase 2 (Part 1) and Phase 3 (Part 2) study. This table includes Part 2 information only.
LS: least squares

Studies 323 (Part 2) and 327 in regional analgesia met their respective primary efficacy endpoints. These studies demonstrated the analgesic efficacy of Exparel 133 mg or 266 mg through 48 to 72 hours. Together, these studies showed that Exparel prolongs the maximum duration of analgesic effect that can be achieved with conventional IR bupivacaine when used as a peripheral nerve block, which has a labelled duration of effect of 4 to 8 hours.

Overall comment on Phase 3 local analgesia studies

Out of 7 studies 4 studies met primary endpoint showing favourable effect of Exparel versus comparator. There was one negative and one positive study in TKA and haemorrhoidectomy. Study in bunionectomy and Caesarean section also were positive.

Overall comment on Phase 3 regional analgesia studies

Out of 4 studies 2 studies met primary endpoint showing favourable effect of Exparel versus comparator. There was one negative and one positive study in TKA. Study in TSA/RCR also were positive. The study in thoracotomy was negative.

The curves of the mean scores over the time showed longer effect of Exparel compared to IR bupivacaine and placebo, however, regarding IR bupivacaine these differences not exceeded time period defined in the primary efficacy endpoint.

The applicant has provided discussion on the possible factors leading to and findings in negative studies. It can be concluded that the applicant has not demonstrated the efficacy of Exparel in all studied pain models. There were limitations of studies, for example add-on design, methodological issues, impact of concomitant therapies, clinical relevance of data, extrapolation from US to EU population etc, that were discussed during the procedure.

Ancillary analyses

Subgroup analyses of the AUC of pain intensity scores were conducted for the positive pivotal Phase 3 Studies: 316, 317, 331, 411 in local analgesia and 323 (Part 2) and 327 in regional analgesia. Some subgroup analyses were underpowered and are generally of marginal importance. Supportive analyses were generally consistent with primary analyses. They are not deemed additive to the body of evidence.

The applicant concluded, that overall, the analyses of subpopulations in pivotal Phase 3 studies in the development programme demonstrate that the long-acting analgesic benefits of Exparel can be expected in both local and regional analgesia across patients of varying age, sex, race, BMI, and geography.

Summary of main efficacy results

Table 24: Summary of efficacy for trial

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Local Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy			
Study identifier	SKY0402-C-316		
Design	Randomised, double-blind parallel-group, placebo-controlled study		
	Duration of main phase:	single intraoperative administration of study drug on Day 1	
	Duration of postanesthesia phase:	72 hours. Postoperative assessment following surgery and immediate postoperative recovery. Subjects remain in the facility for at least 72 hours after administration of study drug.	
	Duration of follow up period after the administration of study drug:	30 days (±4 days) Follow up assessment	
Hypothesis	Superiority		
Treatments groups	Exparel 266 mg (30 mL)	A single dose of study drug was administered intraoperatively via field block at the conclusion of surgery. 96 subjects randomised.	
	Saline (placebo);	94 subjects randomised	
Endpoints and definitions	Primary endpoint	AUC NRS-R ₀₋₇₂ (wWOCF / LOCF)	The primary endpoint is the area under the curve (AUC ₀₋₇₂) of the numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours for subjects receiving Exparel vs. placebo.
	Secondary endpoint	Total consumption of opioid pain medication through 72 hours (mg)	No key secondary endpoints were pre-specified in the study protocol. secondary endpoints related to opioid consumption by treatment group through 72 hours. To evaluate additional efficacy parameters, characterise the safety profile of SKY0402 in comparison with placebo and to assess the pharmacokinetics of clearance of bupivacaine

	Secondary endpoint	Opioid-free through 72 hours	Opioid-free patients through 72 hours
	Secondary endpoint	Time to first use of opioid rescue medication	Time to first use of opioid rescue medication (hours)

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	<ul style="list-style-type: none"> • Safety Population (Safety): The Safety population included all subjects who were randomised and received any amount of study drug. • Full Analysis Set (FA): The FA set included all subjects in the Safety population who underwent the surgical procedure and had sufficient data to compute an NRS-R AUC0-72 (at least 2 NRS-R pain scores after surgery). The FA set was used for the primary analysis. For analyses involving AUCs through other time points, all subjects were included who were in the Safety population, who underwent the surgical procedure, and had sufficient data to compute an NRS-R AUC0-xx. 		
Descriptive statistics and estimate variability	Treatment group	Exparel group 266mg	Placebo
	Number of subjects	94	93
	Primary endpoint AUC NRS-R0-72 Mean (SD)	141.6 (100.6)	202.3 (104.1)
	Secondary endpoint Total consumption of opioid pain medication through 72 hours (mg) Geometric LS Mean	9,9	18,2
	Opioid-free through 72 hours n(%)	26 (27.7)	9 (9.7)

	Time to first use of opioid rescue pain medication (hours)	14.3 (5.2, NE)	1.2 (0.8, 2.8)
Effect estimate per comparison	AUC NRS-R0-72	Comparison groups	Exparel vs Placebo
		Difference, Exparel Placebo (SE)	-60.7 (15.05)
		95% CI	-90.4, -31.0
		P-value	<0.0001
	Secondary endpoint Total consumption of opioid pain medication through 72 hours (mg)	Comparison groups	Exparel vs Placebo
		95% CI	0.55 (0.4, 0.8)
		P-value	0.0006
	Opioid-free through 72 hours	Comparison groups	Exparel vs Placebo
		95% CI	18.0 (6.1, 29.9)
		Cochran-Mantel-Haenszel p-value	0.0007
		Log-rank p-value	<0.0001
	Time to first use of opioid rescue pain medication (hours)		
Title: Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing First Metatarsal Osteotomy (Bunionectomy)			
Study identifier	SKY0402-C-317		

Design	parallel-group, placebo-controlled, randomised, double-blind study	
	Duration of main phase:	single intraoperative administration of study drug on Day 1
	Duration of postanesthesia phase:	24 hours
	Duration of postanesthesia phase Duration of follow up period	72 hours 30 days (\pm 4 days) Follow up assessment
Hypothesis	Superiority	
Treatments groups	Exparel 106 mg (8 mL)	single intraoperative administration of, 97 subjects randomised
	Saline (placebo; 8 mL)	single intraoperative administration 96 subjects randomised
Endpoints and definitions	Primary endpoint	Area under the curve (AUC) of NRS through 24 hours (NRS AUC0-24)
		Evaluate the magnitude and duration of the effect of a single intraoperative administration of Exparel 120 mg, compared with placebo (0.9% sodium chloride for injection) in the reduction of postoperative pain. The primary endpoint was the area under the curve (AUC0-24) of the numeric rating scale (NRS) pain intensity scores through 24 hours for subjects receiving Exparel vs. placebo.

	Secondary endpoint	<p>Opioid-free through 24 hours</p> <p>Total amount of postoperative Percocet use through 24 hours</p> <p>Time to first use of Percocet through 24 hours (hours)</p>	<p>Proportion of subjects who were pain free (defined as an NRS of 0 or 1) at 24 hours and other time points.</p> <ul style="list-style-type: none"> • Proportion of subjects who received no rescue pain medication (Percocet or ketorolac). • Total postoperative consumption, in mg, of Percocet through 24, 36, 48, 60, and 72 hours. • Total amount of postoperative Percocet use through 24, 36, 48, 60, and 72 hours. • Time to first use of Percocet. • Time to first use of IV ketorolac. • Subject's satisfaction with postoperative analgesia at 24 and 72+8 hours.
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Results and Analysis

Analysis description Primary Analysis

Analysis population and time point description	<p>Intent to treat – 24 hours</p> <p>A single dose of study drug was administered intraoperatively via field block at the conclusion of surgery.</p>
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Descriptive statistics and estimate variability	Treatment group	Exparel 106 mg	Placebo	<group descriptor> {as per above terminology}
	Number of subjects	97	96	<n>
	Primary endpoint AUC of NRS-R (0-24)	124.9 (48.32)	146.4 (42.94)	<point estimate>
	Least Squares Mean (SE)	123.9 (4.49)	146.2 (4.59)	<variability>

	Secondary endpoints Opioid-free through 24 hours n (%)	7 (7.2)	1 (1.0)	<point estimate>
	Total amount of postoperative Percocet use through 24 hours (number of tablets), LS Mean	3,8	4,7	<variability>
	Time to first use of Percocet through 24 hours (hours) Subjects who used Percocet, n (%) Median (Q1, Q3)	95 (97.9)	95 (99.0)	<point estimate> <variability>
Effect estimate per comparison	Primary endpoint	Comparison groups	Exparel vs Placebo	
		95% CI	-34.8, -9.8	
		Difference, Exparel Placebo (SE)	-22.3 (6.34)	
		P-value	0.0005	
	Secondary endpoint	Comparison groups	Exparel vs Placebo	
		Opioid-free through 24 hours		
		(95% CI)	6.2 (-19.8, 3.6)	
		P-value	0.0404	
		Total amount of postoperative Percocet use through 24 hours (number of tablets)		
		(95% CI)	-0.9 (-1.6, -0.2)	

		P-value	0.0077
		Time to first use of Percocet through 24 hours (hours)	
		Log-rank p-value	<0.0001
Notes	No key secondary endpoints were pre-specified in the study protocol. The total amount of Percocet rescue medication was lower in the Exparel group than the placebo group and a higher percentage of subjects in the Exparel group were opioid-free.		

<u>Title:</u> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of Exparel for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction		
Study identifier	402-C-329	
Design	Phase 3, randomised, double-blind, placebo-controlled study	
	Duration of main phase:	administered intraoperatively via local administration on Day 1.
	Duration of Run-in phase:	Follow-up from 0 through 48 hours
	Duration of Extension phase:	follow-up visits on Days 7 and 10 on Day 30 for an AE assessment and to inquire if the subject made any unscheduled phone calls or office visits related to pain.
Hypothesis	Superiority	
Treatments groups	Exparel 133 mg in 10 mL	Single administration of Exparel 133 mg in 10 ml; Mode of administration: Infiltration
	Placebo: Normal saline Dosage: Single dose of 10 mL	Single administration of 10 mL Mode of administration: Infiltration 55 was randomised

Endpoints and definitions	Primary endpoint	the area under the curve (AUC) of the NRS pain	To demonstrate the analgesic efficacy of single-dose local administration of Exparel compared with placebo in subjects following bilateral third molar extraction.	
	Secondary endpoints	related to opioid consumption by treatment group	1. The AUC of the NRS pain intensity scores through 24 hours. 2. The AUC of the NRS pain intensity scores through 72 hours. 3. Percentage of opioid-free subjects through 24 hours. 4. Percentage of opioid-free subjects through	
Database lock	28 January 2016			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and	Received study drug, underwent surgery, included under Protocol Amendment. Subjects were randomised in a 2:1 ratio to receive local			
Descriptive statistics and estimate variability	Treatment group	Exparel	Placebo	
	Number of subjects	99	51	
Primary endpoint	AUC NRS-R (0-48)	177.4 (93.62)	180.0 (84.85)	
	LS Mean (SE)	178.9 (10.30)	181.6 (13.63)	
	Secondary endpoints Opioid-free through 48 hours n%	19 (19.2)	12 (23.5)	

	Total opioid consumption through 48 hours LS Mean	6.54 (1.13)	6.12 (1.18)		
	Time to first use of opioid rescue pain medication (hours) Median (Q1, Q3)	3.9 (3.0, 6.9)	3.1 (2.5, 5.4)		
Effect estimate per comparison	Primary endpoint	Comparison groups	Exparel vs Placebo		
		AUC NRS-R (0-48) Difference, Exparel Placebo (SE)	-2.7 (15.76)		
		95% CI	-33.5, 28.2		
		P-value	0.8661		
	Secondary endpoint	Comparison groups	Exparel vs Placebo		
		Opioid-free through 48 hours n (%)			
		(95% CI)	-4.3 (-18.3, 9.7)		
		P-value	0.5390		
		Total opioid consumption through 48 hours (mg)			
		95% CI	1.07 (0.73, 1.56)		
		P-value	0.7347		

		Time to first use of opioid rescue pain medication (hours)	
		Log-rank p-value	0.3696
Notes	The primary efficacy endpoint was not met. There was no statistically significant difference in the percentage of opioid-free subjects, the total consumption of opioid rescue pain medication through 48 hours, or the time to first use of opioid rescue pain medication In the secondary efficacy endpoints.		

Active-controlled studies

Title: Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control Study to Evaluate the Safety And Efficacy of a Single Intraoperative Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty (TKA)		
Study identifier	SIMPLE TKA 311	
Design	Randomised, double-blind, parallel-group, active-controlled study	
	Duration of main phase:	A single dose of study drug was administered intraoperatively via field block on Day 1
	Duration of Run-in phase:	96 hours
	Duration of Extension phase:	Follow-up visits were to be scheduled on Days 10 (± 2) and 36 (± 7).
Hypothesis	Superiority	
Treatments groups	Exparel 532 mg 80 ml	122 were randomised
	IR bupivacaine 177 mg 80 ml	129 were randomised

Endpoints and definitions	Primary endpoint	AUC of the NRS-A from 0 through 72 hours	The primary objective was to demonstrate the superiority of Exparel, compared with IR bupivacaine, with respect to the extent and duration of the analgesic effect achieved by a single intraoperative administration via field block.	
	Secondary endpoint	opioid consumption	The secondary objectives were to evaluate additional efficacy parameters and characterise the safety profile of Exparel in comparison with bupivacaine HCl.	
Analysis description				
Analysis population and time point description	all subjects in the safety subset who underwent the surgical procedure Time point 72 hours			
Descriptive statistics and estimate variability	Treatment group	Exparel 532 mg	IR bupivacaine 177 mg	
	Number of subjects	N=108	N=110	
	Primary endpoint			
	Mean (SD)	359.4 (123.8)	334.9 (113.1)	
	Adjusted Mean (SE)	355.6 (11.1)	332.6 (10.8)	
	Secondary endpoint Consumption of opioid rescue pain medication through 72 hours (mg)			
	Mean (SD)	88.3 (70.6)	83.2 (67.2)	
Adjusted Geometric Mean	62.1	55.0		

	Received opioid rescue pain medication through 72 hours n%	108 (100)	109 (99.1)	
	Time to first use of opioid rescue pain medication (hours) Median (Q1, Q3)	0.6 (0.3, 2.3)	0.6 (0.4, 2.2)	
Effect estimate per comparison	Primary endpoint AUC0-72 of the NRS-A	Comparison groups	Exparel 532 mg vs bupivacaine HCl (with epinephrine) 177 mg	
		Difference, Exparel IR Bupivacaine	23.0	
		95% CI	-6.6, 52.5	
		P-value	0.1266	
	Secondary endpoint	Comparison groups	Exparel 532 mg vs bupivacaine HCl (with epinephrine) 177 mg	
		Consumption of opioid rescue pain medication through 72 hours (mg)		
		95% CI	1.13 (0.9, 1.4)	
		P-value	0.319	

		Received opioid rescue pain medication through 72 hours n (%)	
		95% CI	0.9 (-7, 12)
		p-value	0.340
		Time to first use of opioid rescue pain medication (hours)	
		Log-rank p-value	0.586
Notes	A statistically significant difference between the Exparel and IR bupivacaine groups in AUC NRS-A0-72 was not observed. No key secondary endpoints were pre-specified in the study protocol. No significant differences in the consumption of opioid rescue pain medication or the percentage of subjects who received opioids through 72 hours or the time to first use of opioid rescue pain medication		

Title: Phase 4, multicenter, randomized, double-blind, active-controlled trial in subjects undergoing primary unilateral TKA under spinal anesthesia with bupivacaine hydrochloride (HCl) (10-15 mg).		
Study identifier	402-C-331	
Design	Randomised, double-blind, active-controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	A single dose of study drug was administered at the end of surgery prior to wound closure 48 hours after surgery A follow-up visit was scheduled for all subjects on Day 15. A follow-up on postsurgical Day 30 to assess for AEs.
Hypothesis	Superiority	
Treatments groups	Exparel 266 mg admixed with *IR bupivacaine 89 mg and expanded in saline (total	70 Randomised
	IR bupivacaine 89 mg expanded in saline (total volume of 120 mL)	69 Randomised

Endpoints and definitions	Co-Primary endpoint	AUC VAS (12-48)	to compare pain control and total opioid consumption following local infiltration analgesia
	Co-Primary endpoint	Total Opioid Consumption from 0 to 48 hours	The total postsurgical opioid consumption through 48 hours.
	Secondary endpoint	Opioid-free through 48 hours	The percentage of opioid-free subjects in the Exparel + IR bupivacaine group compare with IR bupivacaine group at 48 hours
		Time to first use of opioid rescue pain medication (hours)	The time to first use of opioid rescue pain medication in the Exparel + IR bupivacaine group compare with IR bupivacaine group through 48 hours
		OBAS at 48 Hours	total overall benefit of analgesia score at 48 hours

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	Efficacy Analysis Set: all subjects in the Safety Analysis Set who underwent the planned surgery. All analyses based on the Efficacy Analysis Set were based on randomised treatment regardless of treatment actually received.			
Descriptive statistics and estimate variability	Treatment group	Exparel 266 mg + IR bupivacaine 89 mg	IR bupivacaine 89 mg	
	Number of subjects	70	69	
	Co-primary endpoint			
	AUC VAS12-48			

	Co-primary endpoint Total Opioid Consumption Geometric LS Mean (SE)	16.3 (6.68)	80.3 (33.25)	
	Secondary endpoints Opioid-free through 48 hours n (%)	7 (10.0)	0	
	Time to first use of opioid rescue pain medication (hours) Median (Q1, Q3)	4.1 (2.6, 9.7)	2.9 (1.0, 7.2)	
	OBAS at 48 Hours Median (Q1, Q3)	4.1 (4.08)	4.6 (4.33)	
Effect estimate per comparison	Co-primary endpoint	Comparison groups	Exparel 266 mg + bupivacaine 89 mg vs	
		Difference, Exparel IR bupivacaine	-26.9	
		95% CI	-56.6, 2.8	
		P-value	0.0381	
	Co-primary endpoint Total Opioid Consumption	Comparison groups	Exparel 266 mg + bupivacaine 89 mg vs bupivacaine 89 mg	

		Ratio, Exparel: IR bupivacaine	0.203
		95% CI	0.065, 0.631
		P-value	0.0029
	Secondary endpoint Opioid-free through 48 hours	Comparison groups	Exparel 266 mg + bupivacaine 89 mg vs bupivacaine 89 mg
		Difference, Exparel IR bupivacaine	0.098
		95% CI	0.0284, 0.1685
		P-value	0.0088
Notes	<p>The cumulative pain scores in the Exparel + IR bupivacaine group were significantly lower than the IR bupivacaine group. The total postsurgical opioid consumption through 48 hours was statistically significantly lower in the Exparel + IR bupivacaine group compared to the IR bupivacaine Group. The percentage of opioid-free subjects was significantly higher in the Exparel + IR bupivacaine group (10%) than the IR bupivacaine group (0%) at 48 hours.</p>		
<p>Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy</p>			
Study identifier	SIMPLE Hemorrhoidectomy 312		
Design	Randomised, double-blind, parallel-group, active-controlled study		
	Duration of main phase:	A single dose of study drug was administered intraoperatively (at the end of surgery) via field block on Day 1.	
	Duration of Run-in phase:	96 hours	
	Duration of Extension phase:	30 days	
Hypothesis	Superiority		

Treatments groups	Exparel 266 mg		109 randomised. A single dose of study drug was administered (at the end of surgery) via field block on Day 1.	
	IR bupivacaine 89 mg (40 mL)		111 was randomised	
Endpoints and definitions	Primary endpoint	NRS-R0-96	AUC of the NRS-R from 0 through 96 hours	
	Secondary endpoint	Opioid consumption	Consumption of opioid pain medication through 96 hours (mg) Received opioid rescue pain medication through 96 hours	
<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
Analysis population and time point	Efficacy Analysis Set: all subjects in the Safety Analysis Set who underwent the planned surgery.			
Descriptive statistics and estimate variability	Treatment group	Exparel 266 mg	IR Bupivacaine 89 mg	
	Number of subjects	99	99	
	AUC NRS-R (0-96)			
	Mean (SD)	395.6 (212.7)	359.1 (194.0)	
	Adjusted Mean (SE)	393.2 (20.5)	352.4 (20.6)	
	Consumption of opioid pain medication through 96 hours (mg)	29.6 (31.97)	26.4 (33.86)	
	Mean (SD) Adjusted metric Mean	13.23	10.38	

	Received opioid rescue pain medication through 96 h hours	n (%) 85 (85.9)	n (%) 80 (80.8)	
	Time to first use of opioid rescue pain medication (hours) Median (Q1, Q3)	12.0 (1.1, 27.6)	11.2 (2.3, 39.0)	
Effect estimate per comparison	Primary endpoint	Comparison groups	Exparel 266 mg vs IR bupivacaine 89 mg	
		Difference, Exparel IR bupivacaine (SE)	40.7 (28.2)	
		95% CI	-14.9, 96.3	
		p-value	0.15	
	Secondary endpoint	Comparison groups	Exparel 266 mg vs IR Bupivacaine 89 mg	
		95% CI	1.28 (0.8, 2.1)	
	Consumption of opioid pain medication through 96 hours (mg)	P-value	0.3354	
	Secondary endpoint	Comparison groups	Exparel 266 mg vs IR bupivacaine 89 mg	
	Received opioid	95% CI	5.1 (-5, 15)	

	rescue pain medication through 96 hours	P-value	0.3404
	Secondary endpoint Time to first use of opioid rescue pain medication (hours)	Log-rank p-value	0.3550
Notes	The relatively low average pain scores in both groups throughout the 96-hour period suggests that the study had low assay sensitivity for evaluating the analgesic benefits of a long-acting local anaesthetic. No significant differences in the consumption of opioid rescue pain medication, the percentage of subjects who received opioids through 96 hours, or the time to first use of opioid rescue pain medication were observed.		

<u>Title:</u> A Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Safety and Efficacy of Exparel When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section		
Study identifier	402-C-411	
Design	Randomised, double-blind, active-controlled study	
	Duration of main phase:	A single dose was administered at the end of surgery no more than 90 minutes after skin incision closure of the Caesarean section.
	Duration of Run-in phase:	72 hours
	Duration of Extension phase:	30 days
Hypothesis	Superiority	
Treatments groups	Exparel 266 mg admixed with *IR bupivacaine 44 mg and expanded in saline	A single dose was administered at the end of surgery no more than 90 minutes after skin incision closure of the Caesarean section. 96 were randomised
	IR bupivacaine 44 mg expanded in saline (total volume of 60 mL)	90 were randomised

Endpoints and definitions	Primary endpoint	Total Postsurgical Opioid Consumption through 72 Hours	Total Postsurgical Opioid Consumption through 72 Hours	
	Secondary endpoint	Time to first use of opioid rescue pain medication	Time to first use of opioid rescue pain medication (hours)	
	Secondary endpoint	Opioid-spared through 72 hours	the percentage of opioid-spared subjects at 72 hours	
	Secondary endpoint	Opioid-free through 72 hours	the percentage of opioid-free subjects at 72 hours	
<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
Analysis population and time point description	all randomised subjects in the safety analysis set who underwent C-section and who also met the study criteria for correct TAP placement, local anaesthetic dosing, and a multimodal post-operative analgesic regimen			
Descriptive statistics and estimate variability	Treatment group	Exparel 266 mg + IR bupivacaine 44 mg	IR bupivacaine 44 mg	
	Number of subjects	71	65	
	Primary endpoint Total Postsurgical Opioid Consumption			
	LS Mean (SE)	15.5 (6.67)	32.0 (6.25)	

	Secondary endpoint Time to first use of opioid rescue pain medication (hours)			
	Median (Q1, Q3)	53.2 (23.4, NA)	41.1 (18.4, NA)	
	AUC VAS0-72 LS Mean (SE)	147.9 (21.13)	178.5 (19.78)	
	Opioid-spared through 72 hours n	38 (53.5)	16 (24.7)	
	Opioid-free through 72 hours LS mean probability	51.9	48.6	
Effect estimate per comparison	Primary endpoint Total Postsurgical Opioid	Comparison groups	Exparel 266 mg + IR bupivacaine vs IR bupivacaine	
		Difference, Exparel - IR bupivacaine	-16.5	
		95% CI	-30.8, -2.2	
		P-value	0.0117	
	Secondary endpoint	Comparison groups	Exparel 266 mg + IR bupivacaine vs IR bupivacaine	

		Log-rank P-value	0.7536
		Difference, Exparel IR bupivacaine	-30.6
		95% CI	-75.9, 14.7
		Non-inferiority p-value	0.002
		Odds ratio, Exparel: IR bupivacaine	3.51
		95% CI	1.56, 7.91
		p-value	0.0012
	Opioid-free through 72 hours	Odds ratio, Exparel:IR bupivacaine	1.14
		95% CI	0.555, 2.341
Notes	<p>The primary efficacy endpoint was met; the LS mean opioid consumption through 72 hours was approximately 52% lower in the Exparel 266 mg + IR bupivacaine 44 mg group compared with the IR bupivacaine 44 mg group. The cumulative pain intensity scores with Exparel 266 mg + IR bupivacaine 44 mg were statistically non-inferior to IR bupivacaine alone from 0 through 72 hours. There were no statistically significant differences observed in the time to first use of</p> <p>opioid rescue medication or the percentage of subjects who were opioid-free.</p>		
<p><u>Regional Analgesia Studies</u></p> <p><u>Placebo-controlled Studies</u></p> <p><u>Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy</u></p>			
Study identifier	402-C-322		
Design	Randomised, double-blind, parallel-group, placebo-controlled study		

	Duration of main phase:	A single dose was administered after the posterolateral thoracotomy was completed (ie, just prior to the surgical site closure).		
	Duration of Run-in phase:	72 hours		
	Duration of Extension phase:	Follow-up Day 12		
		Follow-up Day 30		
Hypothesis	Superiority			
Treatments groups	Exparel 266 mg (20 mL)	A single dose was administered after the posterolateral thoracotomy was completed (ie, just prior to the surgical site closure).		
	Saline (placebo; 20 mL)	95 were randomised		
Endpoints and definitions	Primary endpoint	AUC NRS-R (0-72).	the area under the curve (AUC) of the NRS-R pain intensity scores through 72 hours	
	Secondary endpoint	Regarding opioid consumption	Total postsurgical opioid consumption (in mg) through 72 hours. Time to first opioid administration	
	Secondary other: specify > endpoint	First Use of Opioid Rescue Pain Medication	Time (hours) to First Use of Opioid Rescue Pain Medication	
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	After completing screening procedures, eligible subjects undergoing posterolateral thoracotomy were randomised 1:1 to receive either Exparel or placebo.			
Descriptive statistics and estimate variability	Treatment group	Exparel 266 mg	Placebo	
	Number of subjects	94	91	
	Primary endpoint AUC NRS-R (0-72)	353.8 (156.50)	343.6 (156.41)	

	LS Mean (SE)	472.1 (37.19)	459.0 (36.57)	
	Secondary endpoint Total Postsurgical Consumption (mg) of Opioid Rescue Pain Medication 72 Hours Mean (SD)			
	Median	75.00	70.00	
	Time (hours) to First Use of Opioid Rescue Pain Medication Subjects Administered an Opioid Rescue, n (%)	90 (95.7)	90 (98.9)	
	Median (Q1, Q3)	1.1 (0.7, 3.9)	0.7 (0.4, 1.2)	
Effect estimate per comparison	AUC NRS-R (0-72)	Comparison groups	Exparel 266 mg vs Placebo	
		Difference, Exparel - Placebo (SE)	13.1 (22.39)	
		95% CI	-31, 57	
		P-value	0.5598	
	Time to first opioid rescue (hours)	Comparison groups	Exparel 266 mg vs Placebo	
		Median (Q1, Q3)	1.1 (0.7, 3.9) vs 0.7 (0.4, 1.2)	
		95% CI	[0.92, 1.87] vs [0.58, 0.87]	

Notes	No statistically significant difference between the Exparel and placebo groups in AUC NRS-R0-72 was observed. The mean postsurgical opioid consumption and the time to first use of opioid rescue medication were similar between the
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<u>Title: A Multicenter, Randomized, Double-blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty</u>			
Study identifier	Protocol No: 402-C-323 ClinTrials.gov No: NCT01683071		
Design	A Phase 2/3, Multicentre, Randomised, Double-blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study		
	Duration of main phase:	72 hours – active treatment was administrated 2h prior to TKA (Day 1)	
	Duration of Run-in phase:	30 days	
	Duration of Extension phase:	Some endpoints were assessed at up to Day 30	
Hypothesis	Superiority – <i>Part 2</i>		
Treatments groups (<i>Part 2</i>)	liposome bupivacaine (total of 266 mg in 20 mL)	Active treatment. Single dose, 2h prior to TKA, 99 subjects randomised	
	preservative-free normal saline for injection, 20 mL	Placebo. Single dose, 2h prior to TKA, 97 subjects randomised	
Endpoints and definitions	Primary endpoint	AUC ₀₋₇₂ of the NRS-R Pain Intensity Scores	The AUC of the NRS-R pain intensity scores through 72 hours
	Secondary endpoint	Total postsurgical opioid consumption in mg (0-72h)	Total postsurgical opioid consumption (in mg) through 72 hours
	Secondary endpoint	Time to first opioid rescue (in hours)	Time to first opioid rescue
Database lock	Not found		
<u>Results and Analysis</u>			
Analysis description	Primary Analysis		
Analysis population and time point description	Efficacy analysis set as stated in the dossier: all subjects in the safety analysis set who underwent the planned surgery and was based on randomised treatment, regardless of actual treatment received. Time point: 72 hours		

Descriptive statistics and estimate variability	Treatment group	Liposome bupivacaine	Placebo
	Number of subjects	92	91
	AUC ₀₋₇₂ of the NRS-R Pain Intensity Scores	420.3 (168.81)	514.0 (160.04)
	Mean (SD)		
	LS Mean (SE)	418.9 (16.86)	515.5 (16.95)
	Total postsurgical opioid consumption in mg (0-72h)	76.10	103.32
	Geometric LS Mean		
	Median (min, max)	80.88 (7.4, 295.1)	107.45 (19.4, 328.5)
Time to first opioid rescue (in hours)	92 (100.0)	91 (100.0)	
N (%)			
Effect estimate per comparison	Primary endpoint: AUC ₀₋₇₂ of the NRS-R Pain Intensity Scores	Comparison groups	Liposome bupivacaine 266 mg vs placebo
		LS Mean difference (SE)	-96.5 (23.92)
		95% CI	[-144, -49]
		P-value (ANCOVA)	<0.0001
	Secondary endpoint: Total postsurgical opioid consumption in mg (0-72h)	Comparison groups	Liposome bupivacaine 266 mg vs placebo
		Geometric LSM Ratio liposome bupivacaine vs placebo	0.74
		95% CI	[0.6, 0.9]
		P-value (ANOVA)	0.0016
	Secondary endpoint: Time to first opioid	Comparison groups	Liposome bupivacaine 266 mg vs placebo

	rescue (in hours)	Median (Q1, Q3)	0.44 (0.33, 0.78) vs 0.43 (0.32, 1.07)
		95% CI	[0.400, 0.533] vs [0.367, 0.567]
Notes	Clinical relevance of the results (primary efficacy endpoint and positive secondary one) and the shown effect in lowering AUC NRS-R intensity pain scores of liposome bupivacaine over 72 hours is questionable.		

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Femoral Nerve Block with Exparel for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty			
Study identifier	402-C-326		
Design	Randomised, double-blind, placebo-controlled study		
	Duration of main phase:	drug was administered into the femoral nerve under ultrasound guidance at least one hour prior to surgery	
	Duration of Run-in phase:	108 hours	
	Duration of Extension phase:	30 days	
Hypothesis	Superiority		
Treatments groups	Exparel 133 mg (20 mL)	Single dose, 1h prior to TKA 76 were randomised	
	Exparel 266 mg (20 mL)	Single dose, 1h prior to TKA 77 were randomised	
	Saline (placebo; 20 mL)	Single dose, 1h prior to TKA 79 were randomised	
Endpoints and definitions	Primary endpoint	AUC VAS (0-72)	to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection femoral nerve block with Exparel in subjects undergoing primary unilateral TKA.

	Secondary endpoints	related to opioid consumption by treatment group	Total Postsurgical Opioid Consumption (mg) through 72 Hours (mg)
	Secondary endpoint	related to opioid consumption by treatment group	Opioid-Free subjects through 72 Hours
	Secondary endpoint	related to opioid consumption by treatment group	Time (hours) to First Use of Opioid Rescue Pain Medication

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point	all subjects in the safety analysis set who underwent the planned surgery; analyses and summaries were based on randomised treatment, regardless of			
Descriptive statistics and estimate variability	Treatment group	Exparel 133 mg	Exparel 266 mg	Placebo
	Number of subjects	75	76	79
	Primary endpoint AUC VAS (0-72)	254.6 (176.62)	253.0 (164.22)	282.6 (166.07)
	LS Mean (SE)	259.5 (19.01)	251.0 (18.85)	279.8 (18.49)
	Secondary endpoint Total Opioid Consumption (mg) 72 Hours LS Mean (SE)	161.8 (11.32)	179.9 (12.46)	178.5 (12.11)

	Time (hours) to First Use of Opioid Rescue Medication Median (Q1, Q3)	3.0 (1.8, 5.1)	2.9 (1.5, 5.8)	2.4 (1.1, 3.7)
Effect estimate per comparison	Primary endpoint	Comparison groups	Exparel 133 mg, Exparel 266 mg vs Placebo	
		Difference, Exparel Placebo	-20.2/ -28.8	
		95% CI	[-72.4, 31.9]/ [-80.5, 22.9]	
		P-value	0.446/ 0.275	
	Secondary endpoint	Comparison groups	Exparel 133 mg, Exparel 266 mg vs Placebo	
	Total postsurgical opioid consumption in mg (0-72h)	LS treatment Ratio	0.853/ 0.913	
		95% CI	[0.717, 1.014]/ [0.769, 1.084]	
		P-value	0.072/ 0.300	
	Secondary endpoint	Comparison groups	Exparel 133 mg, Exparel 266 mg vs Placebo	
	Time to first opioid rescue (Hours)	Log-rank p-value	0.190/ 0.255	
Notes	No statistically significant differences between the Exparel groups and the placebo group in AUC VAS0-72 were observed. No statistically significant differences were observed between the Exparel groups and the placebo group for any of the key secondary endpoints.			

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety and Pharmacokinetics of Brachial Plexus Nerve Block with Exparel for Postsurgical Analgesia in Subjects Undergoing Total Shoulder Arthroplasty or Rotator Cuff Repair

Study identifier 402-C-327

Design	Randomised, double-blind, placebo-controlled study		
	Duration of main phase:	single dose was administered into the brachial plexus under ultrasound guidance at least one hour prior to surgery.	
	Duration of Run-in phase:	120 hours	
	Duration of Extension phase:	30 days	
Hypothesis	Superiority		
Treatments groups	Exparel 133 mg (20 mL)	Single dose, 1h prior to TSA or RCR 69 were randomised	
	Exparel 266 mg (20 mL)	Single dose, 1h prior to TSA or RCR 15 were randomised	
	Saline (placebo; 20 mL)	Single dose, 1h prior to TSA or RCR 72 were randomised	
Endpoints and definitions	Primary endpoint	AUC VAS (0-48)	to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection brachial plexus block with Exparel in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.
	Secondary endpoint	Total Opioid Consumption (mg) through 48 Hours	Total Postsurgical Opioid Consumption (mg) through 48 Hours (mg)
	Secondary endpoint	Opioid-Free through 48 Hours	Opioid-Free patients through 48 Hours
	Secondary endpoint	Time (hours) to First Use of Opioid Rescue Medication	Time (hours) to First Use of Opioid Rescue Pain Medication through 48 Hours

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	all subjects in the safety analysis set who underwent the planned surgery; analyses and summaries were based on randomised treatment, regardless of actual treatment received. After enrolment in the study was initiated, newly published data from an investigator-initiated trial became available suggesting that the 133-mg dose of Exparel provided adequate magnitude and duration of analgesic effect, so an administration decision was made to discontinue enrolment in the 266 mg group.			
Descriptive statistics and estimate variability	Treatment group	Exparel 133 mg	Placebo	
	Number of subjects	69	71	
	Primary endpoint AUC VAS (0-48) Mean (SD)	134.2 (98.05)	255.3 (105.03)	
	LS Mean (SE)	136.4 (12.09)	254.12 (11.77)	
	Secondary endpoint Total Opioid Consumption (mg) through 48 H (mg) LS Mean (SE)	25.0 (5.35)	109.7 (22.97)	
	Opioid-Free through 48H N%	9 (13.0)	1 (1.4)	

	Time (hours) to First Use of Opioid Rescue Medication Subjects on Rescue Medication, n (%)	65 (94.2)	70 (98.6)	
	Median (Q1, Q3)	4.2 (0.7, 18.8)	0.6 (0.4, 0.9)	
Effect estimate per comparison	Primary endpoint	Comparison groups	Exparel 133 mg vs Placebo	
		Difference, Exparel Placebo	-117.7	
		95% CI	-150.9, -84.5	
		p-value	<0.0001	
	Secondary endpoint	Comparison groups	Exparel 133 mg vs Placebo	
	Total Opioid Consumption (mg) through 48 H (mg)	Ratio, Exparel: Placebo	0.228	
		95% CI	0.126, 0.411	
		P-value	<0.0001	
	Secondary endpoint	Comparison groups	Exparel 133 mg vs Placebo	
	Opioid-Free through 48 Hours	Difference, Exparel Placebo	0.116	
		95% CI	0.032, 0.200	
		P-value	0.008	
	Secondary endpoint	Log-rank p-value	<0.0001	
	Time (hours) to First Use of			

Notes	<p>After enrolment in the study was initiated, newly published data from an investigator-initiated trial became available suggesting that the 133-mg dose of Exparel provided adequate magnitude and duration of analgesic effect, so an administration decision was made to discontinue enrolment in the 266 mg group.</p> <p>The primary efficacy endpoint was met. The LS mean AUC VAS0-48 was statistically significantly lower in the Exparel 133 mg group than the placebo group. The total postsurgical opioid consumption through 48 hours was statistically significantly lower in the Exparel 133 mg group than the placebo group. The percentage of opioid-free subjects was statistically significantly greater in the Exparel 133 mg group (13%) than the placebo group (1.4%) at 48 hours. The time to first use of opioid rescue pain medication was statistically significantly longer in the Exparel 133 mg group than the placebo group through 48 hours.</p>
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Analysis performed across trials (pooled analyses and meta-analysis)

The applicant did not perform analysis across trials. Moreover, the 11 main Phase 3 studies are highly heterogeneous which precludes any pooling.

Clinical studies in special populations

No formal studies in elderly patients, patients with renal and hepatic impairment were performed.

Elderly

The local and regional analgesia studies included patients 65 years of age and older (up to 88 years). Most of the patients were in age group 65-74, followed by age group 75-85. The age group 85+ included only 7 patients.

The applicant stated that of the 1109 subjects who received EXPAREL in the Local Analgesia Pool, 214 subjects were ≥ 65 years of age and 59 subjects were ≥ 75 years of age. Of the 536 subjects who received EXPAREL in the Regional Analgesia Pool, 255 subjects were ≥ 65 years of age and 63 subjects were ≥ 75 years of age. No adverse drug-related effects with EXPAREL were observed related to older age. Clinical experience with Exparel has not identified differences in efficacy between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Ancillary analysis was performed in the subgroup of patients < 65 years versus ≥ 65 years.

The applicant noted that due to the differences in study designs, durations of treatment, and primary efficacy endpoint definitions, the results cannot be pooled across studies.

The applicant also claimed that in clinical studies, differences in various PK parameters have been observed between elderly and younger individuals. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of Exparel.

Table 25

	Age 65-74 (n=401) n (%)	Age 75-84 (n=107) n (%)	Age 85+ (n=7) n (%)
Controlled Trials	396 (98.8)	107 (100.0)	7 (100.0)
Non-Controlled trials	5 (1.2)	0	0

Renal and hepatic impairment

The applicant relays on the published data and pharmacokinetic study in hepatic impairment study (Study 110).

The applicant stated that bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. This should be considered when performing dose selection of Exparel.

Furthermore, amide-type local anaesthetics, such as bupivacaine, are metabolised by the liver. Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anaesthetic systemic toxicity. Therefore, consider increased monitoring for local anaesthetic systemic toxicity in subjects with moderate-to-severe hepatic disease.

The results of the hepatic impairment study found that the relative magnitude of the differences in PK parameters do not indicate that a dosage adjustment is required for patients with mild to moderate hepatic impairment.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development of Exparel is based on 9 Phase 3 studies (main studies). The studies are grouped according to the type of analgesia studied: 5 main studies in local analgesia (Exparel administered as a field block) and 4 main studies in regional analgesia (Exparel administered as a field block). Two additional studies in local analgesia are designated as supportive (Studies 331 and 411, which had an add-on design to IR bupivacaine). In all main local analgesia studies, a single dose of Exparel was administered at the end of the studied surgical procedure. In all main regional analgesia studies, a single dose of Exparel was administered prior to the studied surgical procedure.

- **Design**

All of the 9 main studies were randomised, double blind, multicentre, active or placebo-controlled trials.

Exparel is visually distinguishable from the comparators (both placebo and bupivacaine HCl). The applicant provided satisfactory explanations regarding varying blinding practices within and across phase 3 clinical studies. Overall a very small number of unblinding events was reported, only 2 such events in Study 411.

Studies were multicentre, and a large number of centres was included across all phase 3 clinical trials. The vast majority of studies were conducted in the US. Only one study was entirely conducted in Europe (316), while three were partially conducted in Europe (322, 326, 327). Out of 1131 patients who received Exparel in the main studies, 373 were from Europe, which is about 33%. The applicant provided a short discussion on the issue of generalisability to the EU population. Multimodal analgesia regimens are used in both the US and EU. However, literature data indicates statistically significant lower pain scores in the first day after orthopaedic surgery and overall less opioids being used in European countries compared to the US. Therefore, the limited benefits observed in clinical studies with Exparel can be expected to be even smaller in everyday clinical practice in Europe.

- **Population**

The following pain models were used in the Phase 3 clinical programme: total knee arthroplasty (311, 331, 323, 326), haemorrhoidectomy (312, 316), bunionectomy (317), third molar extraction (329), caesarean section (411), posterolateral thoracotomy (322), total shoulder arthroplasty/rotator cuff repair (327).

In general, the inclusion and exclusion criteria were consistent with the target population for each surgical model. However, patients with concurrent painful physical conditions were excluded. Patients with knee osteoarthritis and pain arising from both knees could not be included in the TKA studies, since study drug is expected to show a local effect only. The exclusion of these patients is reasonable; however it does not correctly reflect the clinical practice.

- **Comparator**

According to the CHMP Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011), placebo is an acceptable comparator; active comparator of known effectiveness provides context to the measured differences from placebo and facilitates an evaluation of the clinical relevance of those differences.

Regarding results among clinical studies with an **active comparator** (311, 312, 331 and 411) they are not supportive of Exparel. Briefly, studies 311 and 312 failed to show superiority of Exparel over bupivacaine HCl+epinephrine. Study 331 showed statistically significant superiority over comparator while Study 411 confirmed non-inferiority (superiority was not confirmed). However, studies 331 and 411 had an add-on design, in which Exparel+bupivacaine was compared to bupivacaine. The dose of bupivacaine in bupivacaine-only groups is too low to be considered a valid comparator, both in Study 331 and 411. Thus, superiority of Exparel to an active comparator is not robustly demonstrated.

In general, bupivacaine with epinephrine might be a more suitable comparator than bupivacaine without epinephrine, since the former has a more prolonged duration of action and can be administered in higher doses. The applicant failed to scientifically justify not using bupivacaine+epinephrine as a comparator in studies 331 and 411.

None of the studies in regional analgesia setting was performed with an active comparator arm, which makes it difficult to put the observed results in a clinical context, although placebo as a comparator is acceptable.

- **Endpoints and the duration of study**

All of the main Phase 3 studies defined AUC of pain intensity scores and total postoperative opioid use as primary or secondary outcomes. However, the endpoints are remarkably different across studies, as can be seen in the table below.

Table 26: Outcomes regarding AUC of pain intensity scores and opioid use in main Phase 3 studies

Study	Outcomes			
	AUC of pain intensity scores	Total postoperative opioid use	Proportion of opioid-free subjects	Time to first rescue medication
Type of surgery				
311 Total Knee Arthroplasty (TKA)	AUC ₀₋₇₂ of the NRS-A (other timepoints also defined)	Total opioid through 12, 24, 36, 48, 60, 72, 84, and 96 hours	Opioid-free through 12, 24, 36, 48, 60, 72, 84, and 96 hours	Time to first opioid
312 Haemorrhoidectomy	AUC ₀₋₉₆ of the NRS-R (other timepoints also defined)	Total opioid through 12, 24, 36, 48, 60, 72, 84, and 96 hours	Opioid-free through 12, 24, 36, 48, 60, 72, 84, and 96 hours	Time to first opioid
316 Haemorrhoidectomy	AUC ₀₋₇₂ of the NRS-R (other timepoints also defined)	Total opioid through 12, 24, 36, 48, 60, and 72 hours	Opioid-free	Time to first opioid
317 Bunionectomy	AUC ₀₋₂₄ of the NRS-R (other timepoints also defined)	Total consumption, in mg and number of tablets, of Percocet through 24, 36, 48, 60, and 72 hours	Rescue-free	Time to first Percocet; Time to first ketorolac
329 Third Molar Extraction	AUC ₀₋₄₈ of the NRS-R (other timepoints also defined)	N/A	Opioid free through 24, 48, and 72 hours	Time to first opioid
331 Total Knee Arthroplasty (TKA)	AUC ₁₂₋₄₈ of the VAS pain intensity scores (other timepoints also defined)	Total opioid (IV morphine equivalents) from 0 to 48 hours (additionally through 24 hours and 72 hours; and from discharge through Day 29)	Opioid-free at 48 hours (additionally at 24 and 72 hours)	Time to first opioid through 72 hours
411 Cesarean Section	AUC ₀₋₇₂ of the VAS pain intensity score (other timepoints also defined)	Total opioid (oral morphine equivalent dose) through 72 hours	Opioid-free through 72 hours; Opioid-spared through 72 hours	Time to first opioid

		(additionally through 24 and 48 hours, Day 7 and Day 14)		
322 Posterolateral Thoracotomy	AUC ₀₋₇₂ of the NRS-R (other timepoints also defined)	Total opioid through 72 hours; (additionally through 24, 36, 48, and 60 hours)	Rescue-free	Time to first opioid
323 Total Knee Arthroplasty (TKA)	AUC ₀₋₇₂ of the NRS-R (other timepoints also defined)	Total opioid through 72 hours; (additionally through 24, 36, 48, and 60 hours)	Rescue-free	Time to first opioid
326 Total Knee Arthroplasty (TKA)	AUC ₀₋₇₂ of the VAS pain intensity score (other timepoints also defined)	Total opioid (IV morphine equivalents) through 72 hours; (additionally through 24, 48, and 96 hours)	Opioid-free through 72 hours; (additionally through 24, 48, and 96 hours)	Time to first opioid through 72 hours
327 Total Shoulder Arthroplasty or Rotator Cuff Repair (TSA/RCR)	AUC ₀₋₄₈ of the VAS pain intensity score (other timepoints also defined)	Total opioid (IV morphine equivalents) through 48 hours; (additionally through 24 and 48 hours)	Opioid-free through 48 hours; (additionally through 24 and 72 hours)	Time to first rescue through 48 hours

Differences in outcomes and time periods used for primary analyses (that vary from 24 to 96 hours) makes comparisons across studies difficult. Total postoperative opioids are not uniformly defined either. The definition of opioid-sparing in Study 411 is arbitrary and of exploratory value.

Otherwise, outcomes are appropriate and in agreement with the Scientific Advice obtained by NCAs.

- **Baseline analgesics and rescue medication**

Although opioids were generally used as rescue medication in all main Phase 3 studies, differences exist. Permitted analgesics, administered to every patient in the study for providing baseline pain management, varied notably across studies.

Although baseline and rescue medications are generally appropriate, the variability across studies makes comparisons difficult. Study 317 is the only study where a fixed-combination of oxycodone/paracetamol was used as rescue medication. In studies 311, 322 and 323 the use of PCA pumps was permitted.

An evaluation on the impact of concomitant multimodal analgesia on the efficacy of Exparel was provided. Overall, the concomitant therapy was well balanced across treatment groups. At least in some

clinical settings, tramadol would have been used instead of stronger opioids. Tramadol was not utilised in the clinical development programme of Exparel.

- **Methods, Conduct, Analysis**

The **main efficacy population** in local analgesia studies is generally defined as randomised subjects who underwent the surgical procedure, were given study drug and had at least a defined (varying across studies) number of measurements taken in the post-surgical period. The main efficacy population in regional analgesia studies is generally defined as randomised subjects who underwent the surgical procedure and were given the study drug.

Although the definitions of efficacy populations in Phase 3 studies are not entirely in line with the ITT principle, small numbers of randomised patients were excluded from the primary efficacy analyses in the majority of studies. Exclusions are not negligible in 3 studies – Study 311 (11% patients excluded); Study 329 (45.1% patients excluded); Study 411 (27% patients excluded). Since studies 311 and 329 failed to meet their primary endpoint, and adequate explanations were provided, focus remains on post-randomisation exclusions in Study 411 that did meet its primary endpoint.

The absence of a true ITT population is most prominent in **Study 411**, where the applicant defines the Efficacy Analysis set as follows: patients who received study drug, underwent C-section, met criteria for correct TAP placement, local anaesthetic dosing, and a multimodal post-operative analgesic regimen. Patients were excluded not due to non-existing data, and not due to non-existence of pain (like in other Phase 3 studies), but due to not following the protocol strictly. This definition is not in accordance with the ICH E9 Guideline and it resulted in exclusion of 26% randomised patients from Exparel+bupivacaine group and almost 28% of randomised patients from bupivacaine-only group. The applicant was asked to provide re-analysed results using all randomised and treated patients. The re-analysed results show that the statistically significant reduction in the use of opioids through 72 hours observed in Exparel arm was lost when all randomised and treated subjects were included in the analysis. Results for the primary outcome for the re-analyses show a LS mean treatment difference of -2.9 MME with a wide 95% CI that crosses zero (95% CI -15.4 to 9.6) and a p-value of 0.33. No difference between treatment arms was found for any of the secondary outcomes related to the use of opioids in the re-analyses.

Although protocols of studies 316, 317 and 323 allowed for the exclusion of non-responders, no such exclusions were made.

The amount of **missing and imputed data** was provided in line with the Guideline on missing data in confirmatory clinical trials (EMA/CPMP/EWP/1776/99 Rev. 1). In **Study 331**, in the period from 12 to 48 hours, the proportion of missing pain intensity scores was between 11.6% and 52.9% in Exparel+IR bupivacaine group and between 8.7% to 42% in IR bupivacaine group. This is a substantial amount of missing data, and no imputation method is considered to be adequate. Also, there is more missing data in IR bupivacaine than in Exparel+IR bupivacaine group at all timepoints in the designated window of 12 to 48 hours (the difference is from 2.3% to 10.9%). Since the nature of the missing data is unknown (wasn't recorded), the proposed reasons for missing data are hypothetical. Due to a large proportion of missing data with an imbalance in the amount of missing data between treatment arms and without the knowledge of the nature of missing data, results regarding pain scores from study 331 should be interpreted with great caution.

In Study **411**, the proportion of missing pain intensity scores in the period from 6 to 72 hours was between 1.4% and 18.8% in Exparel+IR bupivacaine group and between 1.6% and 23.1% in IR bupivacaine group; no clear pattern in missing data was observed. Therefore, the pre-defined multiple imputation method is adequate for handling missing data. The amount of missing data in studies **323** and **327** is small and therefore of less concern for the validity of study results.

During a pre-defined interim analysis for efficacy and sample size recalculation in Study **411**, criteria for futility were met. However, due to deviations in the use of multimodal analgesia observed in the beginning of the trial, the applicant chose to continue the study and exclude patients enrolled in the beginning of the trial. Then a second, unscheduled interim analysis occurred, with the purpose to evaluate efficacy and sample size. No adjustments for the type I error were performed. Unscheduled unadjusted interim analyses looking into efficacy of a medicinal product are not endorsed in the context of phase 3 clinical trials.

In general, satisfactory justifications for other study conduct issues were provided by the applicant.

Efficacy data and additional analyses

- Key findings and uncertainties

Key findings according to primary secondary outcomes related to opioids will be summarised in the table below. Secondary outcomes regarding opioids will be presented as the applicant presented them in Summary of clinical efficacy (hence, some of them are different from the pre-defined outcomes stated in table below).

Table 27: Main efficacy results across main Phase 3 studies

Study treatment groups	Outcomes – Exparel vs. comparator			
	AUC of pain intensity scores	Total postoperative opioid use	Proportion of opioid-free subjects	Time to first rescue medication
311 Exparel 532 mg vs bupivacaine HCl+epinephrine 177 mg	AUC ₀₋₇₂ of the NRS-A Not observed*	Total opioid through 72 hours Not observed*	Opioid-free through 72 hours Not observed*	Time to first opioid Not observed*
312 Exparel 266 mg vs bupivacaine HCl+epinephrine 89 mg	AUC ₀₋₉₆ of the NRS-R Not observed*	Total opioid through 96 hours Not observed*	Opioid-free through 96 hours Not observed*	Time to first opioid Not observed*
316 Exparel 266 mg vs placebo	AUC ₀₋₇₂ of the NRS-R 30% reduced (sig.¹)	Total opioid through 72 hours 9.9 vs 18.2 mg = 46 % reduction (sig.¹)	Opioid-free through 72 hours 27.7 vs 9.7% = 18% more patients in Exparel group (sig.¹)	Time to first opioid Median time 14.3 vs 1.2 hours = 12 times longer in Exparel group (sig.¹)
317 Exparel 106 mg vs placebo	AUC ₀₋₂₄ of the NRS-R 15% reduced (sig.¹)	Number of tablets of Percocet through 24 hours 3.8 vs 4.7 tablets = 1 less tablet in Exparel group (sig.¹)	Rescue-free through 24 hours 7.2% vs 1% = 6% more in Exparel group (sig.¹)	Time to first Percocet Median time 7.2 vs 4.3 hours = 1.7 times longer in Exparel group (sig.¹)

329 Exparel 133 mg vs placebo	AUC ₀₋₄₈ of the NRS-R Not observed*	N/A	Opioid free through 48 hours Not observed*	Time to first opioid Not observed*
331 Exparel 266 mg + bupivacaine 89 mg vs bupivacaine 89 mg	AUC ₁₂₋₄₈ of the VAS pain intensity scores 13% reduced (sig.¹)	Total opioid (IV morphine equivalents) from 0 to 48 hours 16.3 vs 80.3 mg = 80% reduction (sig.¹)	Opioid-free through 48 hours 10% vs 0% (sig.¹)	Time to first opioid Mean time 4.1 vs 2.9 hours = 1.4 times longer in Exparel group (sig.¹)
411 Exparel 266 mg + bupivacaine 44 mg vs bupivacaine 44 mg	AUC ₀₋₇₂ of the VAS pain intensity score 17% reduction (non-inferiority proven; superiority not achieved)	Total opioid (oral morphine equivalent dose) through 72 hours 15.5 vs 32.0 mg = 51.6% reduction (sig.¹)	Opioid-free through 72 hours Not observed*	Time to first opioid Not observed*
322 Exparel 266 mg vs placebo	AUC ₀₋₇₂ of the NRS-R Not observed*	Total opioid through 72 hours; Not observed*	Rescue-free Not observed*	Time to first opioid Not observed*
323 Exparel 266 mg vs placebo	AUC ₀₋₇₂ of the NRS-R 18.7% reduction (sig.¹)	Total opioid through 72 hours; 76.1 vs 103.32 mg = 26.3% reduction (sig.¹)	Rescue-free Not observed*	Time to first opioid Not observed*
326 Exparel 133 and 266 vs placebo	AUC ₀₋₇₂ of the VAS pain intensity score Not observed*	Total opioid (IV morphine equivalents) through 72 hours Not observed*	Opioid-free through 72 hours; Not observed*	Time to first opioid through 72 hours Not observed*
327 Exparel 133 mg vs placebo	AUC ₀₋₄₈ of the VAS pain intensity score 46.3% reduction (sig.¹)	Total opioid (IV morphine equivalents) through 48 hours 25 vs 109.7 mg = 77.2% reduction (sig.¹)	Opioid-free through 48 hours; 13% vs 1.4% = 11.6% more in Exparel group (sig.¹)	Time to first rescue through 48 hours 4.2 vs 0.6 hours = 7 times longer in Exparel group (sig.¹)

*Not observed = statistically significant difference not observed

Sig.¹ = statistically significant

The applicant discussed the likely reasons for **not meeting the primary endpoint in 5 main studies**. In Study **311** potent IV opioids were used too liberally; post-surgery pain scores were low in Studies **312** and **326**; possible leakage of Exparel was observed in Study **329**; in study **322** too few nerves were blocked for the large incision site and PK data suggests the drug was absorbed and cleared very

quickly, consistent with administration into a highly vascular field. Several general difficulties of conducting studies of local anaesthetics in the surgical setting were identified. One of the main difficulties is the inability to enrich the study population so that it includes only patients with a baseline pain score above a certain level, since the source of pain is the surgical insult, i.e., pain is not present before the surgery. Also, local anaesthetic is applied intraoperatively and prophylactically, and this precludes the ability to titrate the medicinal product. Heterogeneity of the study population that cannot be accounted for before the medicinal product is administered is another identified problem.

Following remarks concern the uncertainties of the results in the studies that reached the primary endpoint:

Study **316** reached statistically significant results over all key outcomes. However, lack of a statistically significant difference concerning PONV-free time, use of antiemetics and postoperative constipation seems to suggest that the reduction in the use of opioids seen in Exparel arm did not translate into a reduction in opioid-related adverse events. As per one of the sensitivity analysis, when wWOCF for rescue pain medication is not applied, the difference in primary outcome did not reach statistical significance.

In Study **331** a statistically significant difference according to the second co-primary outcome (total opioid consumption through 48 hours) was observed. However, the range of total opioid used was very wide in both groups. Patient's perception of pain intensity and opioid-related adverse effects (OBAS questionnaire) was similar in both groups which is surprising given the magnitude of reduction in opioid use. In addition, Study 331 suffered from a large amount of missing data (at times larger than 50% with notable differences between treatment arms) on the first co-primary endpoint (AUC of VAS) making conclusion unreliable. This is confirmed when additional analyses without imputations for missing scores are performed - primary results are no longer statistically significant. Also, the dose of IR bupivacaine in the comparator arm is too low according to clinical practice, and this favours the experimental (Exparel) arm.

Study **411** also suffers from serious methodological issues. The primary efficacy population excludes more than a quarter of all randomised patients. When all randomised and treated patients were analysed, the difference in total opioid use through 72 hours (primary endpoint) in Exparel vs comparator groups was no longer statistically significant. An unplanned interim analysis evaluating efficacy was performed without adjustment for type I error. The dose of IR bupivacaine in the comparator arm is too low according to clinical practice, which favours the experimental (Exparel) arm.

In 3 studies that met their primary endpoint **an issue about opioids** requiring thorough discussion is identified. Out of initially opioid-free patients, more of them allocated to Exparel required an opioid at later timepoints compared to those allocated to the comparator. This was observed in Study **411**, where 4 additional subjects (5.6%) in the Exparel + IR bupivacaine group and 1 additional subject (1.5%) in the IR bupivacaine group who were opioid free at 72 hours received opioid rescue through Day 14. The same pattern is observed in Study **317**, where additional 5 patients (5.1%) who were rescue-free at 24 hours in Exparel group required an opioid from 24-72 hours, while in placebo group no additional patients required rescue medications from 24-72 hours. The same pattern is observed in Study **327**, where additional 12 patients (17.4%) who were opioid-free through 24 hours in Exparel group required an opioid from 24-72 hours, while in placebo group no additional patients required opioids from 24-72 hours. Although numerically more patients in Exparel group required an opioid after the primary timepoint compared to placebo group, the absolute numbers of opioid-free patients and the between-group differences were too small for reliable conclusions to be drawn.

Overall, a lack of consistency of results is observed, both across studies (i.e., the magnitude of results for identical endpoints) and within studies (i.e., the magnitude of reduction in AUC of pain intensity scores does not correspond to the magnitude of reduction in total opioid use). From the discussion

presented by the applicant it can be concluded that background anaesthesia and the type of surgery are not related to the heterogeneous results observed.

Data from a phase 1 Study 109 demonstrate that the expected time to onset of analgesia with Exparel is 2 minutes.

The **duration of analgesic effect** of Exparel shown in clinical studies varies, as presented below.

In Study **316**, 95% CIs of Mean pain intensity scores of Exparel and placebo start to overlap from 12 hours onwards and the difference in the use of opioids is driven by the difference in opioid consumption in the first 24 hours, while opioid consumption in the period from 24 hours to 72 hours is similar in both groups. Therefore, we can say that the observed duration of analgesic efficacy shown for Exparel in Study 316 is **24 hours** (and not 72 hours as claimed by the applicant).

In Study **317**, although 95% CIs of Mean pain intensity scores of Exparel and placebo start to overlap from 8 hours onwards, total opioid use is significantly lower in Exparel compared to placebo during the first 24 hours. Therefore, the duration of analgesic efficacy shown for Exparel in Study 317 is **24 hours**.

In Study **323**, 95% CIs of the Mean pain intensity scores of Exparel and placebo start to overlap from around 8 hours forward (with the exception noted at the 24 hours timepoint). The reduction in total opioids is present through 72 hours in Exparel group, although this reduction is mainly driven by the difference in opioid consumption observed in the first 24 hours. Therefore, the duration of analgesic efficacy shown for Exparel in Study 323 is between **24 and 48 hours**.

In Study **327**, 95% CIs of the Mean pain intensity scores of Exparel and placebo overlap at the 48-hour timepoint, but not before that. Although the timepoint defined as the basis for primary evaluations is 48 hours, a clinically relevant reduction in the use of opioids is achieved for all evaluated periods (i.e., 0-24h, 24-48h and 48-72h). Therefore, the duration of analgesic efficacy shown for Exparel in Study 327 is **72 hours**.

The duration of analgesic efficacy as shown in pivotal phase 3 trials is 24 hours in local analgesia studies and between 24 hours and 72 hours in regional analgesia studies.

- **Magnitude and clinical relevance of the effect**

All of the main Phase 3 studies defined AUC of pain intensity scores and total postoperative opioid use as primary or secondary outcomes. The interpretation of AUC of pain intensity scores is difficult and not straightforward. However, a time-averaged difference >1 in pain intensity scores (i.e., the AUC treatment difference divided by the total time in hours under observation) would be indicative of a clinically significant overall effect although this measure doesn't take into account the magnitude of difference at each time point and disregards the amount of opioids used to achieve the pain intensity scores observed.

A summary of opioid-related outcomes (total postoperative opioid consumption and proportion of opioid-free subjects) through 48 and 72 hours will be presented in the table below, regardless of statistical considerations about hierarchy or multiplicity.

Table 28: Opioid-related outcomes through 48 and 72 hours across main Phase 3 studies

Study treatment groups	Outcomes – Exparel vs. comparator			
	Total postoperative opioid use through 48 hours	Total postoperative opioid use through 72 hours	Proportion of opioid-free subjects through 48 hours	Proportion of opioid-free subjects through 72 hours

311 Exparel 532 mg vs bupivacaine HCl+epinephrine 177 mg	50.58 vs 44.97 mg = Not observed*	62.1 vs 55 mg = Not observed*	0 vs 1.8% = Not observed*	0 vs 0.9% = Not observed*
312 Exparel 266 mg vs bupivacaine HCl+epinephrine 89 mg	8.3 vs 6.41 mg = Not observed*	12 vs 8.77 mg = Not observed*	17.2 vs 22.2% = Not observed*	15.2 vs 19.2% = Not observed*
316 Exparel 266 mg vs placebo	7.7 vs 16.2 mg = 52.5% reduction (sig.¹)	9.9 vs 18.2 mg = 46 % reduction (sig.¹)	Not found	27.7 vs 9.7% = 18% more patients in Exparel group (sig.¹)
317 Exparel 106 mg vs placebo	Number of tablets of Percocet through 48 hours 8 vs 8.3 tablets = Not observed*	Number of tablets of Percocet through 72 hours 11.4 vs 11.3 tablets = Not observed*	No rescue 2.1% vs 1% = Not observed*	No rescue 2.1% vs 1% = Not observed*
329 Exparel 133 mg vs placebo	N/A	N/A	19.2% vs 23.5% = Not observed*	18.2% vs 23.5% = Not observed*
331 Exparel 266 mg + bupivacaine 89 mg vs bupivacaine 89 mg	16.3 vs 80.3 mg = 80% reduction (sig.¹)	18.26 vs 91.4 mg = 80% reduction	10% vs 0% (sig.¹)	10% vs 0% (sig.¹)
411 Exparel 266 mg + bupivacaine 44 mg vs bupivacaine 44 mg	9.1 vs 20.5 mg = 55.6% reduction (sig.¹)	15.5 vs 32.0 mg = 51.6% reduction (sig.¹)	Not found	51.9% vs 48.6% Not observed*
322 Exparel 266 mg vs placebo	57.3 vs 59.3 mg Not observed*	70.9 vs 71.4 mg Not observed*	Not found	4.3% vs 1.1% Not observed*
323 Exparel 266 mg vs placebo	66 vs 89 mg = 25.8% reduction (sig.¹)	76.1 vs 103.32 mg = 26.3% reduction (sig.¹)	Not found	Not observed* All required
326 Exparel 133 and 266 vs placebo	120.4 and 136.2 vs 142.9 mg Not observed*	161.8 and 179.9 vs 178.5 mg Not observed*	Not observed* All required	Not observed* All required

327 Exparel 133 mg vs placebo	25 vs 109.7 mg = 77.2% reduction (sig.¹)	52.15 vs 148.6 mg = 65% reduction (sig.¹)	13% vs 1.4% = 11.6% more in Exparel group (sig.¹)	5.8% vs 1.4% = Not observed*
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*Not observed = statistically significant difference not observed

Sig.¹ = statistically significant

An interpretation encompassing the magnitude and the clinical relevance of the observed results is presented below.

Study 316 (haemorrhoidectomy); Exparel 266 mg vs placebo; primary outcome AUC0-72 of the NRS-R

The observed difference in AUC0-72 of NRS-R was -60.7 points (95%CI -90.4 to -31.0) in Exparel group compared to placebo. This translates into a reduction in AUC of the NRS-R of about 30% over 72 hours, which is consistent with all population values in the range of a 15% to 45% reduction with Exparel compared to placebo. Hypothesis testing yielded a p-value of <0.0001, meaning that the probability of observing such a result if the null hypothesis of no difference between treatments was correct, is very small. When presented as the time-averaged difference in pain intensity scores, this corresponds to a reduction of 0.84 points in the period of 72 hours. Since this is <1, it is not clinically relevant. Regarding pain intensity, 95% CIs of Mean pain intensity scores of Exparel and placebo start to overlap from 12 hours onwards. As per one of the sensitivity analysis, when wWOCF for rescue pain medication is not applied, primary outcome is no longer statistically significant.

Total opioid consumption through 72 hours is significantly lower in Exparel group (9.9 mg vs 18.2 mg of morphine equivalent). However, this result is driven by the difference in opioid consumption in the first 24 hours (5.4 mg in Exparel vs 12.9 mg in placebo), opioid consumption in the period from 24 hours to 72 hours is similar in both groups (4.5 mg in Exparel vs 5.3 mg in placebo). Moreover, lack of a statistically significant difference concerning PONV-free time, use of antiemetics and postoperative constipation through 72 hours (all pre-defined as other efficacy outcomes) suggest that the reduction in the use of opioids seen in Exparel arm did not translate into a clinically measurable benefit in opioid-related adverse events. The proportion of opioid-free patients through 72 hours (27.7% vs 9.7%) and time to first use of opioid (14.3 h vs 1.2 h) favour Exparel over placebo with statistically significant p-values.

In summary, clinical relevance of the primary outcome is not clearly established. Secondary outcomes regarding opioids favour Exparel over placebo but the multiplicity was not accounted for. The overall difference in opioid consumption is driven by the difference in the first 24 hours, after which it becomes similar in both groups. Taken together these results suggest some clinical benefit of Exparel over placebo in the studied setting, but the benefit seems limited to the first 24 hours and the results are not robust.

Study 317 (bunionectomy); Exparel 106 mg vs placebo; primary outcome AUC0-24 of the NRS-R

The observed difference in AUC0-24 of NRS-R was -22.3 points (95% CI: -34.8, -9.8) in the Exparel 106 mg group compared to placebo. This translates into a reduction in AUC of NRS of 15.3% over 24 hours in Exparel group, with is consistent with all population values between a reduction of 23.8% and the reduction of 6.7% seen in Exparel compared to placebo when considering the width of the 95% CI. Hypothesis testing yielded a p-value of 0.0005, meaning that the probability of observing such results if there was no difference between treatments was very small. When presented as the time-averaged difference in pain intensity scores, this corresponds to a reduction of 0.93, which is, at best, of borderline

clinical relevance. Regarding pain intensity, 95% CIs of Mean pain intensity scores of Exparel and placebo start to overlap from 8 hours onwards.

Secondary outcomes related to opioids through 24 hours favour Exparel with statistically significant p-values. However, when considering absolute numbers, the results are not robustly clinically relevant. The benefit in consumption of rescue medication in Exparel groups translates into 1 less tablet of 5 mg oxycodone/325 mg paracetamol FDC through 24 hours, which is consistent with all population values in the range of 1.6 less tablets to 0.2 less tablets in Exparel group. In Exparel group 6.2% more patients remained opioid-free through 24 hours, but the absolute numbers are small (7 patients opioid-free through 24 hours in Exaprel and only 1 in placebo group) leading to a wide 95% CI that crosses zero representing the large uncertainty in the population value. Median time to first use of rescue medication is 2.9 hours shorter in Exparel group compared to placebo.

Additional 5 patients (5.1%) who were rescue-free at 24 hours in Exparel group required an opioid rescue from 24-72 hours, while in placebo group no additional patients required rescue medications from 24-72 hours.

In summary, clinical relevance of the primary outcome is not clearly established. Secondary outcomes regarding opioids favour Exparel over placebo but even with an inflated chance of observing a type I error, the results are hardly clinically relevant.

Study 323, Part 2 (TKA); Exparel 266 mg vs placebo; primary outcome: AUC0-72 of the NRS-R

The primary efficacy endpoint in Study 323, AUC of NRS-R from 0 to 72 hours, was 96.5 points lower in the Exparel 266 mg group than the placebo group (95% CI -144, -49; $p < 0.0001$). This translates to an 18.7% reduction in Exparel group; when considering the width of the 95% CI, we can expect the population value of AUC NRS-R0-72 to be in the range from a 27.9% reduction to a 9.5% reduction in Exparel group compared to placebo. The time-averaged difference in pain intensity scores is 1.3 points over 72 hours. These results are clinically relevant.

Significantly less opioids were consumed in the Exparel arm through 72 hours – the ratio of geometric LS means of total opioids through 72 hours in Exparel: placebo groups is 0.74 (95% CI 0.6, 0.9; p -value 0.0016). This corresponds to a reduction of 26.3%, and when considering the width of the 95% CI the result is consistent with all values in the range of 40% reduction to a 10% reduction in Exparel arm through 72 hours. These results are also clinically relevant. However, the reduction in the total use of opioids in Exparel vs placebo was mainly driven by the difference in the first 24 hours (the difference for 0-24h is 13.82 mg; the difference for 24-48h is 6.21 mg and for 48-72 mg the difference is 4.19 mg). Other outcomes related to opioids were not clinically relevant - all patients in both groups received opioid rescue pain medication by 6.6 hours post-dose; time to first opioid was also similar for both treatment arms.

In summary, overall clinically relevant results from Study 323 are AUC of pain intensity scores through 72 hours and total opioids through 72 hours, although the latter is driven by the difference observed in the first 24-48 hours. Other opioid related endpoints (proportion of opioid-free patients, time to first opioid) are not clinically relevant.

Study 327 (total shoulder arthroplasty/rotator cuff repair [TSA/RCR]); Exparel 133 mg vs placebo; primary outcome: AUC0-48 of the VAS

The primary efficacy endpoint in Study 327, AUC of VAS from 0 to 48 hours (AUC VAS0-48) was 117.7 points lower in the Exparel 133 mg group than the placebo group (95% CI -150.9, -84.5; $p < 0.0001$). This translates to a 46.3% reduction in Exparel group; when considering the width of the 95% CI, we can expect the population value of AUC VAS0-48 to be in the range from a 59.4% reduction to a 33.3%

reduction in Exparel group compared to placebo. Time-averaged difference in pain intensity scores of 2.5 points over 48 hours. These results are clinically relevant.

All results regarding opioids favour Exparel and are clinically relevant – a reduction in total opioids through 48 hours of 77.2% was observed in Exparel arm, consistent with all population values in the range of an 87% reduction to a 60% reduction in Exparel arm. Other secondary outcomes related to opioids also favour Exparel – proportion of opioid-free patients through 48 hours (13% vs 1.4%) and time to first rescue through 48 hours (4.2 vs 0.6 hours).

However, additional 12 patients (17.4%) who were opioid-free through 24 hours in Exparel group required an opioid from 24-72 hours, while in placebo group no additional patients required opioids from 24-72 hours. This can be interpreted as initially favourable effect of Exparel being lost or even becoming unfavourable after 24 hours.

Overall, all primary and key secondary results in Study 327 show a clinically relevant effect in favour of Exparel through 48 hours.

The supportive studies with an add-on design (**331** and **411**) will be briefly mentioned since the interpretation of the results is hampered by internal validity issues and firm conclusion can't be made. The results from Study 331 are not clinically relevant with the exception of total opioid use through 48 hours. Primary efficacy outcome (total opioids used) in Study 411 is no longer statistically significant if all randomised and treated patients are included.

Overall, in the majority of main Phase 3 studies all or nearly all patients required opioid rescue through 72 hours.

In the initial assessment, it was stated that some aspects of reduction in the use of opioids warrant further discussion – e.g. does the observed reduction in total opioid use translate into less opioid-related adverse events, less prolonged opioid use and less opioid dependence. The applicant failed to provide a thorough discussion on this topic, stating that none of the Exparel clinical studies were designed or powered to assess how reductions in opioid consumption would translate into reductions in opioid-related adverse events. The applicant relies on literature data supporting that reductions in opioid use can be expected to provide clinical benefits to patients since many opioid-related adverse events are dose related (Wheeler et al, 2002; Zhao et al, 2004). This is acknowledged; however, due to large reduction in the use of opioids observed in some studies, it was reasonable to expect a reduction in opioid-related adverse effects in those studies. However, although PONV-free time, use of antiemetics and postoperative constipation through 72 hours were all pre-defined as other efficacy outcomes in Study **316**, no difference between treatment arms was observed regardless of the significant reduction in the amount opioids used in Exparel arm. Similarly, in Study **331**, patient's perception of pain intensity and opioid-related adverse effects (OBAS questionnaire) was similar in both groups regardless of the significant reduction in the amount of opioids used in Exparel arm.

In summary, studies 316 and 317 remained as studies that reached their primary endpoint in **local analgesia** setting. Results from Study **316** suggest some clinical benefit of Exparel over placebo in the studied setting, but the benefit seems limited to the first 24 hours and the results are not very robust. Results from Study **317** suggest minor clinical benefit of Exparel over placebo in the studied setting over 24 hours. Clinical relevance of opioid-related outcomes remains unproven.

Studies 323 and 327 remained as studies that reached their primary endpoint in **regional analgesia** setting. Overall clinically relevant results from Study **323** are AUC of pain intensity scores through 72 hours and total opioids through 72 hours, although the latter is driven by the difference observed in the first 24-48 hours. Other opioid related endpoints are not clinically relevant. All primary and key secondary results in Study **327** show a clinically relevant effect in favour of Exparel through 48 hours.

In general, harder to treat patients were excluded from phase 3 trials. Generalisability to the EU population was discussed by the applicant. Since statistically significant lower pain scores in the first day after orthopaedic surgery are noted and less opioids are used in European countries compared to the US, benefits seen in clinical studies with Exparel can be expected to be smaller in everyday clinical practice in Europe.

Dose-effect relationship is not entirely consistent across studies.

Indication

The initially proposed indication was unacceptable for several reasons. The claim “reduction in need for opioids” relates to study endpoints, rather than condition to be treated and therefore was removed from the indication. It is also unacceptable to include comparisons with other medicinal product so original proposal to compare Exparel to IV bupivacaine was removed as well.

Furthermore, CHMP concluded that the indication of Exparel should be based on results from those pivotal studies that reached statistical significance.

In relation to the nerve block indication, it was agreed to focus the indication on the type of the nerve block itself rather than the type of the surgery. In that respect, efficacy and safety are considered to be shown for interscalene brachial plexus and femoral nerve block. The applicant was asked to discuss further if extrapolation to other types of peripheral nerve blocks would be justified. The generalisability from interscalene brachial plexus block to other subtypes of brachial plexus block can be supported. The proposed indication for nerve block includes also femoral nerve block without extrapolation to other types of peripheral nerve blocks, which is agreed.

In relation to the field block indication, it was agreed to limit the indication based on the size of the surgical wound, since statistically significant pivotal studies were performed in small to medium-sized surgeries. The applicant provided a list of examples of other small to medium-sized surgeries where the product could be used based on the same field block technique as in Studies 316 and 317.

The final indication was agreed as follows: *Exparel liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of postoperative pain in adults, and as a field block for treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults (see section 5.1).*

In addition, the following was placed in the Section 4.4 of SmPC:

Efficacy and safety have not been established in major abdominal, vascular and thoracic surgeries.

2.6.4. Conclusions on clinical efficacy

Exparel clinical development programme included pain models only in the post-surgical setting. The majority of pain models were of somatic pain with only 2 studies in a mixed somatic and visceral pain (one in thoracic and one in abdominal surgery). However, studies in thoracic and abdominal surgery were not supportive of the claimed indication, since the thoracic surgery study yielded negative results and the supportive abdominal surgery study was of add-on design and is of limited value due to methodological issues.

The clinical development programme was broad and lengthy, with some of the main Phase 3 studies completed more than 10 year ago. Although robust and consistent results were not observed across the entire phase 3 programme, several of Phase 3 studies have shown clinically relevant results.

Based on the overall clinical programme and the lack of robustness of the results, extrapolation to all local analgesia and all regional analgesia settings was not supported. The final indication is primarily based on the 4 studies that demonstrated clinical efficacy and clinical relevance.

Clinical safety

Patient exposure

Across 35 studies in the Exparel clinical development programme, a total of 2321 individuals were exposed to Exparel (612 healthy subjects in Phase 1 studies, 18 special population subjects in a Phase 1 study, and 1645 subjects in the intended target population in Phase 1, 2 and Phase 3 studies) at doses ranging from 9 to 665 mg.

Table 29

Pool	EXPAREL, N						IR Bupivacaine, N	Placebo, N
	<133 mg	133 mg	>133 mg - <266 mg	266 mg	>266 mg	All Doses		
Combined	169	322	99	764	291	1645	625	604
Local Analgesia	146	153	75	458	277	1109	604	247
Regional Analgesia	23	169	24	306	14	536	21	357

IR = immediate-release

Safety data are summarised using the Safety Population from each respective study, defined as all enrolled subjects who received at least one (full or partial) dose of study medication according to the actual treatment received.

Table 30

Pool	Number of Subjects	Studies Included ^a
Combined Pool	EXP: 1645 BUP: 625 PBO: 604	21 studies 117, 118, 201, 203, 207, 208, 209, 210, 211, 311, 312, 315, 316, 317, 322, 323 (Part 1 and 2) ^b , 326, 327, 329, 331, 411
Local Analgesia Pool	EXP: 1109 BUP: 604 PBO: 247	14 studies 117, 201, 207, 208, 209, 210, 311, 312, 315, 316, 317, 329, 331, 411
Regional Analgesia Pool	EXP: 536 BUP: 21 PBO: 357	7 studies 118, 203, 211, 322, 323 (Part 1 and 2) ^b , 326, 327

BUP=bupivacaine; EXP=EXPAREL; PBO=placebo

Combined Pool

The Combined Pool includes all 21 studies in the Exparel clinical development programme that were conducted in local and regional analgesia for the management of acute pain. This pool is used to evaluate the overall safety profile of Exparel in adults for the proposed indication. Of the 21 studies in the Combined Pool, 2 (117 and 118) were PK and tolerability studies, one (211) was a dose-finding study, seven (316, 317, 322, 323, 326, 327, and 329) were placebo-controlled studies, and 11 (201, 203, 207, 208, 209, 210, 311, 312, 315, 331, and 411) were active-controlled studies. The studies were conducted in a variety of surgical models across a range of Exparel doses from 66 mg to 532 mg. Surgical models include breast augmentation, bunionectomy, haemorrhoidectomy, hernia repair, open posterior spinal fusion or reconstructive surgery, RCR/TSA, third molar extraction, thoracotomy, and TKA.

Local Analgesia Pool

The Local Analgesia Pool includes all 14 studies in the Exparel clinical development programme that were conducted in local analgesia for the management of acute pain. This pool is used to evaluate the safety profile of Exparel when used as a field block to provide local analgesia in adult subjects.

Of the 14 studies in the Local Analgesia Pool, one (117) was a single-arm, open-label PK and initial tolerability study, three (316, 317, and 329) were placebo-controlled studies, and ten (201, 207, 208, 209, 210, 311, 312, 315, 331, and 411) were active-controlled studies. In two studies (331 and 411), Exparel was admixed with IR bupivacaine, with IR bupivacaine also used as an active comparator.

The studies were conducted in a variety of surgical models across a range of Exparel doses from 66 mg to 532 mg. Surgical models include breast augmentation, bunionectomy, haemorrhoidectomy, hernia repair, open posterior spinal fusion or reconstructive surgery, third molar extraction, and TKA.

Regional Analgesia Pool

The Regional Analgesia Pool includes all seven studies in the Exparel clinical development programme that were conducted in regional analgesia for the management of acute pain. This pool is used to evaluate the safety profile of Exparel when used as a peripheral nerve block to provide regional analgesia in adult subjects. Of the seven studies in the Regional Analgesia Pool, one (118) was a single-arm, open-label PK and tolerability study, four (322, 323, 326, and 327) were placebo-controlled studies, and two (203 and 211) were active-controlled studies. The studies were conducted in a variety of surgical models across a range of Exparel doses from 66 mg to 310 mg. Surgical models include bunionectomy, RCR/TSA, posterolateral thoracotomy, and TKA.

Demographic and Other Characteristics of the Study Population

Local Analgesia Pool

In the Local Analgesia Pool, most subjects were <65 years of age, had an ASA class of 1-2, and were white. Most subjects were from the US, although approximately 17% of subjects were from the EU. The distribution of males and females varied across the Exparel dose groups due to the underlying subject populations of some of the studies, but both male and female subjects were represented in each dosing group.

Regional Analgesia pool

In the Regional Analgesia Pool, 55% of subjects were <65 years of age, approximately 70% of subjects had an ASA class of 1-2, and most subjects were white. Approximately 55% of subjects in the Regional Analgesia Pool were from the US and approximately 42% of subjects were from the EU. The distribution of sex by group was similar for the all Exparel and placebo groups, but there was a higher proportion of females than males in the IR bupivacaine group.

So, the presented exposure to Exparel is rather extensive. Overall, the safety database includes a total of 2321 individuals exposed to Exparel (including 612 healthy subjects in Phase 1 studies and 18 special population subjects in a Phase 1 study) at doses ranging from 9 to 665 mg.

1645 patients were exposed to Exparel in the combined pool (1109 patients were exposed to EXPAERL in LA pool and 536 in RA pool). In the combined pool most of patients were 40 – 65 years old (44.1%), slightly lower exposure to Exparel was in patients < 40 years (27.2%) and 65-75 years (21.1%), significantly lower exposure to Exparel was in the age > 75 years. Similar demographic trends were reported in IR bupivacaine and placebo groups. There was a difference in the age distribution between RA and LA pools. Patients were significantly younger in LA pool compared to RA pool. This may be due to the type of surgery. Also, a higher proportion of patients was exposed to Exparel in the LA pool (1109) compared to RA pool (536). Due to the much higher importance of LA in postoperative pain

management it is understood why only 536 subjects in RA pool vs 1109 in LA pool were exposed. No paediatric patients were studied yet.

Adverse events

Treatment-emergent adverse events (TEAEs)

Table 31: Overview of TEAE by treatment group (Combined pool)

Category	EXPAREL					All Doses (N=1645)	IR Bupivacaine (N=625)	Placebo (N=604)
	<133 mg (N=169)	133 mg (N=322)	>133 mg - <266 mg (N=99)	266 mg (N=764)	>266 mg (N=291)			
Total Number of TEAE	335	1124	111	1750	872	4192	1385	1552
Total Number of TESAE	8	10	2	60	19	99	29	50
Number of Subjects with at Least One TEAE, n (%)	106 (62.7)	300 (93.2)	55 (55.6)	505 (66.1)	228 (78.4)	1194 (72.6)	434 (69.4)	438 (72.5)
Number of Subjects with at Least One TESAE, n (%)	5 (3.0)	9 (2.8)	2 (2.0)	42 (5.5)	16 (5.5)	74 (4.5)	24 (3.8)	31 (5.1)
Number of Subjects with at Least One Related TEAE, n (%)	21 (12.4)	151 (46.9)	13 (13.1)	60 (7.9)	25 (8.6)	270 (16.4)	65 (10.4)	97 (16.1)
Number of Subjects with at Least One Severe TEAE, n (%)	14 (8.3)	5 (1.6)	3 (3.0)	39 (5.1)	19 (6.5)	80 (4.9)	32 (5.1)	34 (5.6)
Number of Subjects with at Least One TEAE Leading to Discontinuation of the Study, n (%)	0	0	0	3 (0.4)	1 (0.3)	4 (0.2)	3 (0.5)	8 (1.3)
Number of Subjects with TEAE Leading to Death, n (%)	0	0	0	2 (0.3)	1 (0.3)	3 (0.2)	1 (0.2)	4 (0.7)

IR=immediate-release; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event

Source: [Appendix B, Table 3.3.1.1](#)

Common Adverse Events

Combined Pool

**Table 32: Summary of common (incidence $\geq 2\%$) TEAEs by Treatment group and PT
(Combined pool)**

Preferred Term	EXPAREL					All Doses (N=1645) n (%)	IR Bupivacaine (N=625) n (%)	Placebo (N=604) n (%)
	<133 mg (N=169) n (%)	133 mg (N=322) n (%)	>133 mg - <266 mg (N=99) n (%)	266 mg (N=764) n (%)	>266 mg (N=291) n (%)			
Number of Subjects with at Least One Common TEAE	95 (56.2)	287 (89.1)	45 (45.5)	455 (59.6)	202 (69.4)	1084 (65.9)	392 (62.7)	395 (65.4)
Nausea	64 (37.9)	123 (38.2)	19 (19.2)	225 (29.5)	116 (39.9)	547 (33.3)	223 (35.7)	186 (30.8)
Constipation	23 (13.6)	47 (14.6)	13 (13.1)	115 (15.1)	69 (23.7)	267 (16.2)	111 (17.8)	73 (12.1)
Vomiting	36 (21.3)	45 (14.0)	8 (8.1)	98 (12.8)	34 (11.7)	221 (13.4)	67 (10.7)	103 (17.1)
Pyrexia	12 (7.1)	47 (14.6)	4 (4.0)	95 (12.4)	35 (12.0)	193 (11.7)	34 (5.4)	65 (10.8)
Pruritus	4 (2.4)	15 (4.7)	1 (1.0)	86 (11.3)	17 (5.8)	123 (7.5)	61 (9.8)	56 (9.3)
Hypoaesthesia oral	2 (1.2)	111 (34.5)	0	8 (1.0)	0	121 (7.4)	0	64 (10.6)
Dysgeusia	0	92 (28.6)	0	23 (3.0)	0	115 (7.0)	0	53 (8.8)
Dizziness	19 (11.2)	24 (7.5)	4 (4.0)	44 (5.8)	19 (6.5)	110 (6.7)	33 (5.3)	73 (12.1)
Headache	9 (5.3)	25 (7.8)	4 (4.0)	25 (3.3)	10 (3.4)	73 (4.4)	36 (5.8)	27 (4.5)
Motor dysfunction	0	35 (10.9)	0	35 (4.6)	0	70 (4.3)	1 (0.2)	37 (6.1)
Anaemia	4 (2.4)	2 (0.6)	0	22 (2.9)	36 (12.4)	64 (3.9)	33 (5.3)	13 (2.2)
Hypotension	3 (1.8)	17 (5.3)	2 (2.0)	18 (2.4)	19 (6.5)	59 (3.6)	21 (3.4)	20 (3.3)
Oedema peripheral	0	11 (3.4)	1 (1.0)	18 (2.4)	21 (7.2)	51 (3.1)	17 (2.7)	8 (1.3)
Tachycardia	0	11 (3.4)	0	18 (2.4)	19 (6.5)	48 (2.9)	20 (3.2)	10 (1.7)
Insomnia	1 (0.6)	6 (1.9)	0	21 (2.7)	19 (6.5)	47 (2.9)	22 (3.5)	19 (3.1)

Preferred Term	EXPAREL					All Doses (N=1645) n (%)	IR Bupivacaine (N=625) n (%)	Placebo (N=604) n (%)
	<133 mg (N=169) n (%)	133 mg (N=322) n (%)	>133 mg - <266 mg (N=99) n (%)	266 mg (N=764) n (%)	>266 mg (N=291) n (%)			
Urinary retention	4 (2.4)	6 (1.9)	1 (1.0)	31 (4.1)	5 (1.7)	47 (2.9)	6 (1.0)	22 (3.6)
Muscle twitching	2 (1.2)	22 (6.8)	0	22 (2.9)	0	46 (2.8)	0	29 (4.8)
Muscle spasms	1 (0.6)	7 (2.2)	0	18 (2.4)	16 (5.5)	42 (2.6)	17 (2.7)	8 (1.3)
Anaemia postoperative	0	7 (2.2)	0	15 (2.0)	14 (4.8)	36 (2.2)	18 (2.9)	10 (1.7)
Fatigue	5 (3.0)	8 (2.5)	0	17 (2.2)	6 (2.1)	36 (2.2)	4 (0.6)	15 (2.5)
Hypertension	3 (1.8)	4 (1.2)	2 (2.0)	20 (2.6)	2 (0.7)	31 (1.9)	8 (1.3)	21 (3.5)
Confusional state	6 (3.6)	3 (0.9)	0	15 (2.0)	5 (1.7)	29 (1.8)	4 (0.6)	14 (2.3)
Back pain	0	6 (1.9)	3 (3.0)	12 (1.6)	6 (2.1)	27 (1.6)	21 (3.4)	2 (0.3)
Anxiety	0	4 (1.2)	0	10 (1.3)	12 (4.1)	26 (1.6)	3 (0.5)	6 (1.0)
Hypokalaemia	0	8 (2.5)	0	15 (2.0)	3 (1.0)	26 (1.6)	9 (1.4)	14 (2.3)
Hyperhidrosis	1 (0.6)	1 (0.3)	0	19 (2.5)	4 (1.4)	25 (1.5)	3 (0.5)	16 (2.6)
Hypoaesthesia	0	9 (2.8)	1 (1.0)	6 (0.8)	9 (3.1)	25 (1.5)	10 (1.6)	3 (0.5)
Chills	1 (0.6)	2 (0.6)	0	10 (1.3)	11 (3.8)	24 (1.5)	8 (1.3)	3 (0.5)
Somnolence	5 (3.0)	7 (2.2)	0	8 (1.0)	4 (1.4)	24 (1.5)	4 (0.6)	5 (0.8)
Bradycardia	3 (1.8)	1 (0.3)	4 (4.0)	8 (1.0)	7 (2.4)	23 (1.4)	6 (1.0)	6 (1.0)
Blood loss anaemia	0	2 (0.6)	0	4 (0.5)	16 (5.5)	22 (1.3)	14 (2.2)	1 (0.2)
Pruritus generalised	8 (4.7)	6 (1.9)	0	8 (1.0)	0	22 (1.3)	5 (0.8)	20 (3.3)
Oropharyngeal pain	1 (0.6)	4 (1.2)	2 (2.0)	9 (1.2)	5 (1.7)	21 (1.3)	9 (1.4)	4 (0.7)

Preferred Term	EXPAREL					All Doses (N=1645) n (%)	IR Bupivacaine (N=625) n (%)	Placebo (N=604) n (%)
	<133 mg (N=169) n (%)	133 mg (N=322) n (%)	>133 mg - <266 mg (N=99) n (%)	266 mg (N=764) n (%)	>266 mg (N=291) n (%)			
Dyspepsia	1 (0.6)	4 (1.2)	0	8 (1.0)	6 (2.1)	19 (1.2)	5 (0.8)	8 (1.3)
Procedural pain	1 (0.6)	1 (0.3)	2 (2.0)	4 (0.5)	10 (3.4)	18 (1.1)	16 (2.6)	0
Muscle contractions involuntary	0	17 (5.3)	0	0	0	17 (1.0)	0	12 (2.0)
Pain in extremity	1 (0.6)	3 (0.9)	0	6 (0.8)	7 (2.4)	17 (1.0)	12 (1.9)	2 (0.3)
Erythema	1 (0.6)	4 (1.2)	0	1 (0.1)	7 (2.4)	13 (0.8)	4 (0.6)	1 (0.2)
Hyponatraemia	1 (0.6)	0	0	6 (0.8)	6 (2.1)	13 (0.8)	3 (0.5)	1 (0.2)
Cough	0	3 (0.9)	2 (2.0)	2 (0.3)	5 (1.7)	12 (0.7)	2 (0.3)	0
Dysuria	0	1 (0.3)	2 (2.0)	7 (0.9)	2 (0.7)	12 (0.7)	4 (0.6)	2 (0.3)
Haemoglobin decreased	0	1 (0.3)	0	4 (0.5)	6 (2.1)	11 (0.7)	2 (0.3)	7 (1.2)
Lethargy	0	1 (0.3)	0	2 (0.3)	8 (2.7)	11 (0.7)	0	0
Post procedural oedema	0	10 (3.1)	0	0	0	10 (0.6)	0	8 (1.3)
Blood glucose increased	0	1 (0.3)	0	2 (0.3)	6 (2.1)	9 (0.5)	1 (0.2)	1 (0.2)
Hepatic enzyme increased	0	7 (2.2)	0	1 (0.1)	0	8 (0.5)	0	3 (0.5)
Dry mouth	1 (0.6)	0	2 (2.0)	3 (0.4)	1 (0.3)	7 (0.4)	0	4 (0.7)

IR=immediate-release; TEAE=treatment-emergent adverse event

Source: [Appendix B, Table 3.3.1.3.1](#)

Events were coded using MedDRA version 22.0. AEs are presented in descending order of frequency.

Table 33: Overall summary of TEAE by Relationship to study drug (Combined pool)

SYSTEM ORGAN CLASS Preferred Term	Relationship	EXPAREL					All Doses (N=1645) n (%)	IR Bupivacaine (N=625) n (%)	Placebo (N=604) n (%)
		<133 mg (N=169) n (%)	133 mg (N=322) n (%)	>133 mg <266 mg (N=99) n (%)	266 mg (N=764) n (%)	>266 mg (N=291) n (%)			
Number of Subjects with at Least One TEAE	Related	21 (12.4)	151 (46.9)	13 (13.1)	60 (7.9)	25 (8.6)	270 (16.4)	65 (10.4)	97 (16.1)
	Not Related	85 (50.3)	149 (46.3)	42 (42.4)	445 (58.2)	203 (69.8)	924 (56.2)	369 (59.0)	341 (56.5)

Local Analgesia Pool

The overall incidence of TEAEs was lower for the All Exparel (66.0%) when compared with IR bupivacaine (70.2%), and higher than the placebo group (56.3%). The incidence of TESAEs was higher in the IR bupivacaine group (4.0%) than the All Exparel (2.7%) and placebo (0.8%) groups. The incidence of related TEAEs was lower in the IR bupivacaine group (10.4%) than in the All Exparel (17.6%) and placebo (25.5%) groups. The incidence of severe TEAEs was also higher in the IR bupivacaine group (5.1%) than the All Exparel (4.6%) and placebo (2.4%) groups. There were 3 or fewer TEAEs leading to study drug discontinuation in all groups. There were two deaths reported in the Local Analgesia Pool (one subject in the Exparel 532 mg group and one subject in the IR bupivacaine 150 mg group) that were not considered related to study drug.

There was a higher incidence of TEAEs and related TEAEs in the Exparel 133 mg group than in the other dose groups. Study-level comparisons between Exparel 133 mg and the respective comparator group(s) in each relevant study (i.e., placebo or IR bupivacaine) determined that there were no meaningful differences between the Exparel and comparator groups at the study level.

In Study 209, there was a lower incidence of subjects who experienced at least one TEAE in the All Exparel group (20.3%) compared to IR bupivacaine (42.3%). In Study 317, a higher proportion of subjects reported TEAEs in the placebo group (67.7%) compared to the All Exparel group (59.8%). In Study 331, a higher proportion of subjects reported TEAEs in the Exparel+bupivacaine group (64.3%) compared to the IR bupivacaine group (56.5%). In Study 411, a higher proportion of subjects reported TEAEs in the Exparel+bupivacaine group (63.9%) compared to the IR bupivacaine group (56.2%). In all other studies, the percentage of subjects with at least one TEAE was similar between groups.

Regional Analgesia Pool

Of the 914 subjects in the Regional Analgesia Pool, only 21 subjects received IR bupivacaine; thus, the sample size of the IR bupivacaine group may not provide enough sensitivity to make a meaningful comparison.

The incidence of TESAEs was similar between the All Exparel (8.2%) and placebo (8.1%) groups. The incidence of related TEAEs was higher in the All Exparel group (14.0%) when compared with placebo (9.5%).

The incidence of severe TEAEs was higher in the placebo group (7.8%) than in the All Exparel (5.4%). The incidence of TEAEs leading to study drug discontinuation was higher in the placebo group (2.0%) than in the All E There were six deaths reported in the Regional Analgesia Pool. No TEAEs leading to study drug discontinuation or death were reported in the IR bupivacaine group. No clear dose-related trends were observed among subjects who received Exparel. There was a higher incidence of TEAEs and related TEAEs in the Exparel <133 mg and 133 mg groups than in the other dose groups. Study-level comparisons between Exparel <133 mg and 133 mg and the respective comparator group(s) in each relevant study (i.e., placebo or IR bupivacaine) determined that there were no meaningful differences between the Exparel and comparator groups at the study level. In general, the overall incidence of TEAEs in the Regional Analgesia Pool was higher than the incidence of TEAEs in the Local Analgesia Pool in both

the Exparel 266 mg and the placebo groups. This is due in large part to the different surgeries evaluated in field block studies versus nerve block studies and their corresponding patient populations.

The Regional Analgesia Pool included older subjects with a mean age approximately of 63 years who tended to be more complicated patients undergoing thoracotomy, TKA, bunionectomy, and RCR/TSA compared with the Local Analgesia Pool, which included subjects with a mean age of approximately 47 years who were typically undergoing less invasive procedures.

A higher percentage of Exparel-treated subjects (59.6%) versus placebo-treated (40.5%) subjects experienced TEAEs in Study 322 (posterolateral thoracotomy). The highest incidence of TEAEs was reported in the two TKA studies (323 and 326).

Vital Signs

There were no clinically relevant differences in vital sign results between the All Exparel, IR bupivacaine, and placebo groups when assessed as either absolute values, change from baseline, or shifts from normal at baseline to values outside the normal range following treatment for the Combined Pool, Local Analgesia Pool, and Regional Analgesia Pool.

Electrocardiograms

The effect of Exparel on ECG parameters has been evaluated in two QT studies in healthy volunteers at supra-therapeutic doses as well as with ECG monitoring in all Exparel clinical studies.

Overall, both thorough QT studies found no effect of therapeutic or supra-therapeutic doses of Exparel on cardiac repolarisation.

Combined Pool

The percentage of subjects with a post-treatment ECG interpreted as clinically significant abnormal was 3.5% in the All Exparel group, 3.9% in the IR bupivacaine group, and 0% in the placebo group in the Combined Pool. Study 323 collected normal or abnormal (no further interpretation regarding clinical significance); the percentage of subjects with a post-treatment ECG interpreted as abnormal was 32.7% in the All Exparel and placebo groups. Additionally, the percentage of subjects with a normal ECG at baseline and an abnormal ECG post-treatment (either not clinically significant or PCS) was similar among the treatment groups and no relationship with Exparel dose was observed.

Local Analgesia Pool

The percentage of subjects with a post-treatment ECG interpreted as clinically significant abnormal was 7.8% in the All Exparel group, 3.4% in the IR bupivacaine group, and 0% in the placebo group in the Local Analgesia Pool. In Study 323, the percentage of subjects with a post-treatment ECG interpreted as abnormal was 3.7% in the All Exparel and 3.4% in the placebo group.

Additionally, the percentage of subjects with a normal ECG at baseline and an abnormal ECG post-treatment (either not clinically significant or PCS) was similar among the treatment groups and no relationship with Exparel dose was observed.

Regional Analgesia Pool

The percentage of subjects with a post-treatment ECG interpreted as clinically significant abnormal was 0.5% in the All Exparel group, 5.3% in the IR bupivacaine group, and 0% in the placebo group in the Regional Analgesia Pool. In Study 323, the percentage of subjects with a post-treatment ECG interpreted as abnormal was 29.0% in the All Exparel and 29.3% in the placebo group. Additionally, the percentage of subjects with a normal ECG at baseline and an abnormal ECG post-treatment (either not clinically significant or PCS) was similar among the treatment groups and no relationship with Exparel dose was observed.

Electrocardiogram and Holter Results from Studies 322 and 323

Holter recordings were collected in Studies 322 and 323, and these recordings have undergone substantial additional review and analyses. There were no clinically relevant imbalances between the active study drug (liposome bupivacaine) and placebo for heart rate range, supraventricular or ventricular arrhythmias or bradycardic arrhythmias including sinus pauses > 3 sec; AV block, or mean low heart rate.

Wound Status and Wound Healing

Wound status was assessed in four Phase 2 studies (Study 201, Study 207, Study 208, Study 210) and three Phase 3 studies (Study 311, Study 315, Study 317). A blinded health care provider assessed erythema, drainage, oedema, and induration using a structured scale for each type of assessment on Day 8 or Day 10, and on Day 30 or Day 36, depending on the study. There were no clinically meaningful differences between the Exparel and comparator (IR bupivacaine or placebo) groups in wound status assessments at any time point. Detailed results can be found in the CSR for each study. Satisfaction with wound healing was assessed in three Phase 2 studies (Study 207, Study 208, Study 210) and four Phase 3 studies (Study 311, Study 315, Study 316, Study 317). A blinded care provider assessed their satisfaction with wound healing using a 10-point Likert scale on Day 8 or Day 10, and on Day 30 or Day 36, depending on the study. In all studies, mean wound healing satisfaction scores were high in the Exparel and comparator (IR bupivacaine or placebo) groups at all time points. Detailed results can be found in the CSR for each study.

TEAEs Specific to Regional Analgesia

The applicant has discussed TEAEs: falls and sensory and motor function relating to regional analgesia separately. According to the applicant, the consequences of sensory and motor loss have broader implications on mobility and other functions. Targeting more proximal nerves introduces the need to assess the relative differences in effect on sensory and motor blockade.

In the Regional Analgesia Pool, the incidence of fall was 2.2% in the All Exparel group and 0.3% in the placebo group. The incidence of fall was similar in the Exparel 133 mg (2.4%) and Exparel 266 mg (2.6%) groups. All TEAEs of fall among Exparel subjects in the regional analgesia programme occurred in the TKA studies (323 and 326); the single fall among placebo subjects occurred in the TSA/RCR study (327). Sensory and motor function loss and return with Exparel were assessed in two clinical studies (326 and 327).

As almost all reported falls are attributable to regional analgesia setting in TKA, this setting bears additional safety concern. Sensory and motor functions were assessed in 2 studies, Phase 3 (TKA and TSA/RCR). Persistent loss of function was not reported. The applicant provided graphical presentations of results (please refer to Clinical AR), but all x-axis variables are shown to 192 hours, while assessments were performed until Day 10, and motor loss in Study 327 has not been shown. There was no evidence of long-term sensory loss. Sensory loss was dose-dependent according to one study (326). There were difficulties in assessment of motor function due to immobilisation following surgery and willingness to perform the function test according to the applicant. However, motor loss is worrisome and it is noticed during early phases of clinical development that it was not dose-dependent, rather variable between doses of Exparel.

Presented findings are put in the context of effects on ability to drive and use machines as the effects were shown to last longer than for up to 72 hours.

Serious adverse events and deaths

Deaths

Across the 21 clinical studies, eight deaths were reported: three subjects with Exparel (0.2%), one subject with IR bupivacaine (0.2%), and four subjects with placebo (0.7%).

Combined Pool

A TEAE leading to death occurred in eight subjects in the clinical development programme. Of the eight deaths, three occurred in the All Exparel group, one in the IR bupivacaine group, and four in the placebo group. Two deaths (one Exparel, one IR bupivacaine) occurred in Study 208 (TKA); both were deemed by the study investigator as not related to the study drug. Six deaths (two Exparel, four placebo) occurred in Study 322 in the setting of posterolateral thoracotomy, which was the most invasive procedure evaluated in the development programme; all were considered by the study investigator as not related to the study drug. No deaths were reported in Phase 1 and Phase 4 studies of Exparel.

Fatal adverse events were reported for eight subjects. Three subjects died in Exparel group, one in LA group and two in RA group. As for all deaths no relationship to study drug has been found by investigators.

Other Serious Adverse Events

The percentage of subjects in the Combined Pool experiencing at least one TESAE was similar for the All Exparel group (74/1645 [4.5%]) compared to the IR bupivacaine group (24/625 [3.8%]) and the placebo group (31/604 [5.1%]). No individual TESAE occurred with an incidence of $\geq 0.5\%$ in the All Exparel group and no dose-related trends with Exparel were observed. None of the TESAEs in any group was considered by the investigator as being related to study drug.

TEAEs leading to study discontinuation were rare in the clinical programme. Four subjects who received Exparel (0.2%) and 8 subjects who received placebo (1.3%) discontinued due to a TEAE. None of the TEAEs leading to study discontinuation in any group was considered by the investigator as being related to study drug.

Combined Pool

The percentage of subjects in the Combined Pool experiencing a TESAE was similar for the All Exparel (4.5%) group compared to IR bupivacaine (3.8%) and placebo (5.1%). No individual TESAE occurred with an incidence of $\geq 0.5\%$ in the All Exparel group. None of the TESAEs was considered by the investigator as being related to Exparel. No meaningful differences in the incidence of individual TESAEs were observed among the All Exparel, IR bupivacaine, and placebo groups, and no Exparel dose-related trends were observed.

Local Analgesia Pool

The percentage of subjects in the Local Analgesia Pool experiencing at least one TESAE was lower for the All Exparel (2.7%) group when compared to IR bupivacaine (4.0%) and higher than placebo (0.8%). No individual TESAE occurred with an incidence of $\geq 0.5\%$ in the All Exparel group. None of the TESAEs was considered by the investigator as being related to Exparel. No meaningful differences in the incidence of different TESAEs were observed among the All Exparel, IR bupivacaine, and placebo groups, and no Exparel dose-related trends were observed.

The incidence of TESAEs was similar among the All Exparel, IR bupivacaine, and placebo groups in Study 311.

Regional Analgesia Pool

The percentage of subjects in the Regional Analgesia Pool experiencing at least one TESAE was similar for the All Exparel group (8.2%) compared to placebo (8.1%), with both groups being higher than IR bupivacaine (0.0%). No individual TESAE occurred with an incidence of 1.0% or higher in the All Exparel

group. None of the TESAEs was considered by the investigator as being related to study drug. No meaningful differences in the incidence of different TESAEs were observed between the All Exparel and placebo groups, and no Exparel dose-related trends were observed. The limited sample size of the IR bupivacaine group in the Regional Analgesia Pool precludes meaningful interpretations of the relative frequency of rare events such as TESAEs.

Most TESAEs occurred in Study 322 in posterolateral thoracotomy, which was the most invasive surgery evaluated in the clinical programme. The incidence of TESAEs was similar between the All Exparel and placebo groups.

The rate of SAEs was low in each of the treatment groups. Percentage of subjects experiencing at least one serious TEAE was similar across treatment groups (4.5% Exparel ALL Dose group vs 3.8% IR bupivacaine group and 5.1% placebo). The highest number of serious TEAEs was reported in study 311 for TKA surgery (9.8% in Exparel group vs 12.2% in IR bupivacaine group) and study 208 for TKA surgery (4.8% in Exparel group vs 8.8% in IR bupivacaine group). As such, it was concluded that the Exparel group was superior to the IR bupivacaine group in terms of having lower proportion of subjects with serious TEAEs.

Laboratory findings

In the Combined Pool, there were no clinically relevant differences between the All Exparel, IR bupivacaine, and placebo groups for haematology or clinical chemistry laboratory parameters when assessed as either absolute values, change from baseline, or shifts from normal at baseline to values outside the normal range following treatment. No dose-related trends with Exparel were observed for any laboratory abnormality. There was also no hepatotoxicity signal observed and no cases in any group that met Hy's law criteria for drug-induced liver injury.

Safety in special populations

Intrinsic Factors

Age

In the Combined Pool, approximately 40-50% of All Exparel (726/1645, 44.1%), IR bupivacaine (260/625, 41.6%), and placebo (309/604, 51.2%) subjects were aged 40 to <65 years. The next largest age group was subjects aged <40 years, with 448/1645 All Exparel (27.2%), 228/625 IR bupivacaine (36.5%), and 129/604 placebo (21.4%) subjects in the Combined Pool. The remaining subjects were in the 65 to <75 years (21.2% All Exparel, 15.5% IR bupivacaine, and 20.4% placebo), 75 to <85 years (7.1% All Exparel, 5.9% IR bupivacaine, and 6.5% placebo), and ≥85 years (0.3% All Exparel, 0.5% IR bupivacaine, and 0.7% placebo) age categories. In the Combined Pool, the proportions of subjects with TEAEs, severe TEAEs, or TESAEs were somewhat lower in subjects <65 years of age than in those ≥65 years of age for the All Exparel, IR bupivacaine, and placebo groups and. A small number of subjects had a TEAE leading to discontinuation or death, making it difficult to draw conclusions concerning age-related patterns across the treatment groups. As would be expected, falls were more commonly reported among older subjects. Of the 16 subjects in the All Exparel groups who had a TEAE of fall, six were aged 40 to <65 years (0.8%), five were aged 65 to <75 years (1.4%), four were aged 75 to <85 years (3.4%), and one was aged ≥85 years (20.0%).

Of the 1109 subjects who received Exparel in the Local Analgesia Pool, 214 subjects were ≥65 years of age and 59 subjects were ≥75 years of age. Of the 536 subjects who received Exparel in the Regional Analgesia Pool, 255 subjects were ≥65 years of age and 63 subjects were ≥75 years of age. No adverse drug-related effects with Exparel were observed related to older age. Clinical experience with Exparel has not identified differences in efficacy or safety between elderly and younger patients, but greater

sensitivity of some older individuals cannot be ruled out. In clinical studies, differences in various PK parameters have been observed between elderly and younger individuals. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of Exparel.

Sex

In the Combined Pool, there were greater percentages of female than males in the All Exparel (890/1645, 54.1% vs. 755/1645, 45.9%), IR bupivacaine (414/625, 66.2% vs. 211/625, 33.8%), and placebo (322/604, 53.3% vs. 282/604, 46.7%) groups. There were no clinically significant differences in the proportions of subjects with TEAEs, severe TEAEs, or TESAEs between males and females for the All Exparel, IR bupivacaine, and placebo groups.

Race

Most subjects in the Combined Pool (1416/1645, 86.1% All Exparel, 529/625, 84.6% IR bupivacaine, 527/604, 87.3% placebo) were white. Therefore, the conclusions that can be drawn concerning the impact of race on the TEAE profile are limited. Nevertheless, there were no apparent differences in the proportions of subjects with TEAEs, severe TEAEs, or TESAEs among subjects who were white compared with those who were not white.

ASA Class

In the Combined Pool, the majority of subjects (1171/1645, 71.2% All Exparel, 497/625, 79.5% IR bupivacaine, 435/604, 72.0% placebo) had a baseline ASA Class of 1-2. As expected, the proportion of subjects with TEAEs or TESAEs was higher in subjects with baseline ASA Class 3-4 than in those with a baseline ASA Class 1-2 but no clinically significant differences were noted among the treatment groups and no clinically significant difference as a function of ASA class was observed in the proportion of subjects with a TEAE leading to discontinuation or death. Of the 16 Exparel-treated subjects who had a TEAE of fall, ten had an ASA Class 3-4 at baseline.

Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. This should be considered when performing dose selection of Exparel.

Hepatic Impairment

Amide-type local anaesthetics, such as bupivacaine, are metabolised by the liver. Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anaesthetic systemic toxicity. Therefore, consider increased monitoring for local anaesthetic systemic toxicity in subjects with moderate-to-severe hepatic disease.

Extrinsic Factors

Given that Exparel is intended for single administration as a field block or as a peripheral nerve block, external factors such as tobacco use, alcohol use, and food habits are not expected to have an impact on safety.

Safety related to drug-drug interactions and other interactions

Drug Interactions

Using Exparel followed by other bupivacaine formulations has not been studied in clinical trials. Formulations of bupivacaine other than should not be administered within 96 hours following administration of Exparel. Some physicochemical incompatibilities exist between Exparel and certain other drugs. Direct contact of Exparel with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering Exparel characteristics and potentially affecting the safety and efficacy of Exparel. Therefore, admixing Exparel with other drugs prior to administration is not recommended.

- The administration of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more. Bupivacaine HCl administered together with Exparel may impact the PK and/or physicochemical properties of Exparel, and this effect is concentration dependent. Therefore, bupivacaine HCl and Exparel may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine HCl solution to Exparel does not exceed 1:2. If preparing admixture, the total amount of bupivacaine used (Exparel liposomal + bupivacaine HCl) should not exceed 400 mg equivalents of bupivacaine HCl.
- The toxic effects of these drugs are additive, and their administration should be used with caution including monitoring for neurologic and CV effects related to local anaesthetic systemic toxicity.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before Exparel is administered into the site. Exparel should not be allowed to come into contact with antiseptics such as povidone iodine in solution.
- The administration of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more.
- Studies conducted with Exparel demonstrated that the most common implantable materials (polypropylene, polytetrafluoroethylene, silicone, stainless steel, and titanium) are not affected by the presence of Exparel any more than they are by saline. None of the materials studied had an adverse effect on Exparel. The toxic effects of local anaesthetics are additive and their co-administration, taking into account the extended PK profile of Exparel, should be used with caution, including monitoring for neurologic and cardiovascular effects related to local anaesthetic systemic toxicity.
- Bupivacaine other than Exparel should not be administered within 96 hours following administration of Exparel. Patients that are administered local anaesthetics may be at increased risk of developing methaemoglobinemia when concurrently exposed to the following oxidising agents:

Table 34

Class	Examples
Nitrates/Nitrites	nitroglycerin, nitroprusside, nitric oxide, nitrous oxide
Local anesthetics	benzocaine, lidocaine, bupivacaine, mepivacaine, tetracaine, prilocaine, procaine, articaine, ropivacaine
Antineoplastic agents	cyclophosphamide, flutamide, rasburicase, isofamide, hydroxyurea
Antibiotics	dapsone, sulfonamides, nitrofurantoin, para-aminosalicylic acid
Antimalarials	chloroquine, primaquine
Anticonvulsants	phenytoin, sodium valproate, phenobarbital
Other drugs	acetaminophen, metoclopramide, sulfa drugs (ie, sulfasalazine), quinine

Bupivacaine

Bupivacaine HCl administered together with Exparel may impact the PK and/or physicochemical properties of Exparel, and this effect is concentration dependent. Therefore, bupivacaine HCl and Exparel may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine HCl solution to Exparel does not exceed 1:2. If preparing admixture, the total amount of bupivacaine used (Exparel liposomal + bupivacaine HCl) should not exceed 400 mg equivalents of bupivacaine HCl.

Non-Bupivacaine Local Anaesthetics

Exparel should not be admixed with local anaesthetics other than bupivacaine. Non-bupivacaine-based local anaesthetics, including lidocaine, may cause an IR of bupivacaine from Exparel if administered together locally. The administration of Exparel may follow the administration of lidocaine after a delay of 20 minutes or more. There are no data to support administration of other local anaesthetics prior to administration of Exparel. Other than bupivacaine as noted above, Exparel should not be admixed with other drugs prior to administration.

Evaluable information on interactions is limited to the information provided for currently authorised bupivacaine and presented in the proposed Exparel SmPC. According to the applicant, drug-drug interaction profile for Exparel was mainly based on known bupivacaine interactions with other medicinal products. In this Summary particular attention was paid to potential incompatibilities with liposomal bupivacaine formulation resulting in rapid increase of free bupivacaine. Safety information for Exparel related to potential drug-drug interactions in this Summary of Clinical Safety is identical to that included in the product SmPC.

Discontinuation due to AES

Incidence of AEs that Led to Discontinuation from the Study

TEAEs leading to study discontinuation were rare in the clinical programme. Four subjects who received Exparel (0.2%) and 8 subjects who received placebo (1.3%) discontinued due to a TEAE. None of the TEAEs leading to study discontinuation in any group was considered by the investigator as being related to study drug.

Combined Pool

The incidence of TEAEs leading to study discontinuation was low in all groups: 0.2% in the All Exparel group, 0.5% in the IR bupivacaine group, and 1.3% in the placebo group.

Local Analgesia Pool

There was one (0.9%) TEAE leading to study discontinuation in the All Exparel group, three (0.5%) in the IR bupivacaine group, and one (0.4%) in the placebo group.

Regional Analgesia Pool

The incidence of TEAEs leading to withdrawal was low in all groups: 0.6% in the All Exparel group, 0.0% in the IR bupivacaine group, and 2.0% in the placebo group.

Number of adverse events leading to discontinuation from investigational product was low in all study groups (0.2% in the All Exparel group, 0.5% in the IR bupivacaine group, and 1.3% in the placebo group).

Post marketing experience

According to the applicant, the adverse reactions reported during post-marketing are consistent with those observed in clinical studies and most commonly involve the following SOCs: Injury, Poisoning, and

Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy, pain), Skin And Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest). Review of these events against the current approved US labelling for Exparel has not identified any new safety concerns and no changes to the product labelling have been required for safety reasons since initial approval.

The applicant has addressed the post-marketing experience, including LAST and lack of efficacy, in the product information as requested by the assessors.

2.6.5. Discussion on clinical safety

The submitted safety results are summarised from all subjects who received study drug in the 21 clinical studies (2 Phase 1 studies, 7 Phase 2 studies, and 12 Phase 3 studies – two of which were classified as Phase 4 in the US) conducted in the population of adult individuals who underwent a surgical procedure. In all 21 studies, subjects were administered a single dose of study drug. Safety data are summarised by three safety pools (Combined local and regional analgesia, Local analgesia and Regional analgesia pool) and according to the actual treatment received by the subject.

Safety assessment primarily considering combined pooled analysis set as the experience available from all patients exposed is explored, the whole dose range is of concern and the same safety profile is expected in local and regional analgesia settings.

Safety data set of interest seems sufficiently large to characterise a safety and tolerability profile of liposome bupivacaine (1645 subjects were exposed to single dose of liposome bupivacaine in range of doses, 66 to 532 mg through developmental programme; N of subjects exposed to bupivacaine HCl was 625 (44 to 177 mg); N of subjects exposed to placebo was 604). Drug is intended to be administered as a single dose. Total proposed dose of bupivacaine expressed as free base ranges from 106 to 354.6 mg.

Safety data are collected from the range of local and regional analgesia procedures. The **target population** is adequately reflected as initially proposed indication is limited (please refer to the Clinical efficacy section).

Overall, all adult age groups were represented through drug development. 27% of subjects exposed to the study drug were in <40 years age group, most (44%) were in 40-65 years age group, 28.5% were elderly subjects (65-85 years). There were slightly lesser male subjects when looking to all doses liposome bupivacaine data. Most of the subjects belonged to ASA class 1-2. As discussed in clinical efficacy sections, **the EU safety pool was remarkably smaller** (26% EU subjects, 72% US ones). This raises a concern regarding cultural differences, differences in subjective dimension of pain sensation and regional differences in opioid use. Although total number of TEAEs was lower among EU subjects than US ones, the percentages of subjects with at least one TESAEs, with at least one TEAEs leading to discontinuation of the study and death were higher in the EU than the US population. Participants were acceptably well-balanced regarding baseline **body weight/BMI**. The applicant provided analysis of subjects' **medical history** with responses to the D120 LoQ. Numerous pre-existing disorders reflect broad population status. There were some differences in medical history among treatment group, but none is considered to substantially influence the safety profile.

Overall, percentages of subjects with at least one TEAE did not differ among the all doses liposome bupivacaine, bupivacaine HCl and placebo group, and they are overall high (around 72%). In placebo group there were higher numbers of subjects with at least one TEAE leading to discontinuation of the study and death, but numbers are very small to conclude actual difference. Regarding other TEAE categories there is also no emergent difference. It is visible, though, from the presented data that **266 mg and higher doses** of liposome bupivacaine were associated with higher numbers of subjects with at least one TESAe and severe TEAE, higher numbers of subjects with at least one TEAE leading to

discontinuation of the study and death. On the other hand, smaller doses of liposome bupivacaine were associated with higher numbers of subject with at least one related TEAE. Recorded numbers of subjects with at least one TEAE obviously vary pronouncedly between different studies in local and regional analgesia settings. No firm conclusions can be made. No clear trend of recorded TEAEs between different studies in same setting (according to surgery type) and between different settings (local and regional analgesia settings) were observed. Safety profile could be variable depending on the on the surgery type and different analgesia setting. Incidences of some TEAEs are remarkably different in compared studies, but no firm conclusion can be drawn and no precautionary measures can be given. This observation increases level of uncertainty to overall safety profile of the new drug formulation.

Most commonly reported TEAEs in combined pool: nausea (33.3%), constipation (16.2%), vomiting (13.4%), pyrexia (11.7%) and pruritus (7.5%).

Number of common AEs were reported with higher frequencies for liposome bupivacaine compared to placebo: nausea, constipation, anaemia, oedema peripheral, tachycardia, muscle spasms, anaemia postoperative, back pain, hypoesthesia, chills, oropharyngeal pain, pain in extremity, dysuria.

Number of common AEs were reported with higher frequencies for liposome bupivacaine compared to bupivacaine HCl: vomiting, hypoesthesia oral, dysgeusia, dizziness, motor dysfunction, muscle twitching, confusional state, hyperhidrosis, pruritus generalised, dyspepsia, muscle contractions involuntary, haemoglobin decreased, post procedural oedema, hepatic enzyme increased, dry mouth.

Furthermore, number of common AEs were reported with higher frequencies for liposome bupivacaine compared both to bupivacaine HCl and placebo: pyrexia, anxiety, somnolence, bradycardia, erythema, hyponatraemia, lethargy and blood glucose increased.

Although bupivacaine is an active substance with established safety profile, applicant was asked to elaborate how the formulation and higher doses correspond with safety profile in responses to the D120 LoQ. Significant number of reported AEs have higher frequencies in comparison to bupivacaine HCl and/or placebo. Higher incidence of somnolence was attributable to Study 208 (TKA); higher incidence of bradycardia was attributable to Study 326; higher incidence of pyrexia was attributable to Studies 208, 311, 322, 323, and 326, but the in-study rates were comparable to comparators; higher incidence of dizziness was contributed to the amalgamation paradox when the studies were pooled; higher incidence of muscle spasm was attributable to Study 331, and is chance finding according to the applicant; hepatic enzyme elevations occurred in Study 326; in studies where pruritus generalised was reported, the incidence rates with Exparel and the respective comparator group were similar. As expected, combined safety analysis pool gives somewhat distorted incidences of some adverse events, but additional analyses confirmed that.

It seems that Exparel in the **regional analgesia setting** has somewhat inferior safety profile in comparison to the local analgesia setting.

No apparent emergent **severe** TEAE with notably higher incidence in liposome bupivacaine groups is noticed. Number of severe TEAEs were reported only in all doses of liposome bupivacaine group (combined safety pool). They were reported with low frequencies, but they are mostly reported for higher doses (≥ 266 mg) of liposome bupivacaine.

Dysgeusia and hypoaesthesia oral were **most common ADRs** based on their relationship to study drug administration and the incidence of $\geq 5\%$. When analysing **related** TEAEs by SOCs in the combined pool, it is visible that higher percentages of AEs were assessed as related in all doses liposome bupivacaine group in comparison to bupivacaine HCl and/or placebo pertaining to particular SOCs (cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, investigations, nervous system disorders). Those findings suggest worse safety profile of liposome bupivacaine in comparison to bupivacaine HCl and placebo. Particularly

worrisome are cardiac and nervous system disorders as they pronouncedly differ from bupivacaine HCl and/or placebo. Furthermore, higher percentage of related TEAEs was reported for all doses of liposome bupivacaine in regional analgesia pool in comparison to bupivacaine HCl and placebo, suggesting worse safety profile of liposome bupivacaine in regional analgesia setting. Among different doses of liposome bupivacaine, 133 mg dose had the highest percentage of related TEAEs (around 50%) while for other doses between 8 and 13% of related TEAEs were reported. The applicant was asked to provide discussion on noted discrepancy of related TEAEs percentages among different doses of liposome bupivacaine. The most significant difference was observed for motor dysfunction TEAE (133 mg group 20.7% vs 13.1% All dose group, 0 IR bupivacaine group and 10.4% placebo group). The applicant was initially asked to discuss underlying reasons for substantially higher incidence of motor dysfunction TEAE reported in 133 mg dose group for RA pool. When data are stratified by the studies where the motor dysfunction were mainly reported, there are no discrepancies among different Exparel doses and the numbers are similar to placebo group.

The applicant identified specific issues related to regional analgesia. As almost all reported **falls** are attributable to regional analgesia setting in TKA, this setting bears additional safety concern. Warning on use as a femoral nerve block if early mobilisation and ambulation is part of the patient's recovery plan has been proposed and it is supported.

Studies of ECG effects for healthy volunteers did not indicate clinically relevant QT effects using supra-therapeutic doses of Exparel. Clinically significant ECG deviations were observed in both bupivacaine groups (3.5% in All dose Exparel group and 3.9% IR bupivacaine dose) and were not reported in placebo group for the combined safety pool. No relationship with EPAREL dose was observed. These findings did not reveal any new safety issues and are in line with already established safety profile for bupivacaine. It must be noted that similar results for post-treatment EEG interpreted as significant abnormal were reported for Exparel and IR bupivacaine groups in the Combined safety pool (3.5% vs 3.9%). In the RA pool the percentage of subjects with a post-treatment ECG interpreted as clinically significant abnormal was lower in Exparel group compared to IR bupivacaine group (0.5% vs 5.3%). While in the LA pool percentage of ECG interpreted as clinically significant abnormal was notably higher in Exparel group compared to IR bupivacaine group (7.8% vs 3.4%). The applicant was asked to explain reasons for substantially higher percentage of post-treatment significant abnormal ECG in LA group. The applicant explained that the higher percentage of post-treatment ECGs read as clinically significant abnormal in the Exparel group relative to the IR bupivacaine group in the Local Analgesia (LA) pool was due to the imbalance of abnormal readings at baseline. Prior to study drug administration (i.e. baseline), the rate of clinically significant abnormal ECG readings was 5.2% (22/425) in the Exparel group and 0.9% (2/212) in the IR bupivacaine group. The imbalance in baseline ECG readings persisted during follow-up but was not meaningfully affected by study drug.

Overall, most of the post-treatment ECGs interpreted as clinically significant abnormal in the Exparel and IR bupivacaine groups were also read as clinically significant abnormal at baseline prior to study drug administration. The imbalance in the percentage of subjects with clinically significant abnormal ECG readings was also present at baseline, prior to study drug administration. The percent of subjects with post-treatment ECGs who had a new clinically significant abnormal ECG finding was similar in the All Exparel and IR bupivacaine groups in the LA pool (2.3% vs 1.7%).

Based on known safety profile of bupivacaine and reported TEAEs, the **adverse events of special interest** would be those associated with cardiotoxicity, neurotoxicity and possibly LAST-related ones (although no cases of LAST were identified by the applicant). The applicant initially failed to identify AEs of special interest in the summary of clinical safety, somewhat diminishing safety issues of the drug.

Analyses by the SOCs did not reveal major safety issue. However, cardiac and neurological disorders were common, especially neurological disorders that were observed in one quarter of Exparel

participants. Analysis of AEs, which could be consistent with LAST, was presented in the response to the D120 LoQ. Presented data by SOCs of interest suggest that there was no major difference between treatment groups. Nevertheless, as the AEs of special interest (i.e. cardiotoxicity, neurotoxicity, LAST) for Exparel, that could be life threatening, are found to be common with ones for bupivacaine HCl and other local anaesthetics, the applicant proposes PI communication as risk minimisation measures for the AEs of special interest.

Fatal cases occurred in 2 studies: study 208 (TKA, Phase 2, Local analgesia pool) and study 322 (posterolateral thoracotomy, Phase 3, Regional analgesia pool). 3 were reported in liposome bupivacaine group, 1 in bupivacaine HCl group and 4 in placebo group. Study investigators considered all 8 fatal cases not related to the study drug. In all three fatal cases in liposome bupivacaine groups, higher doses were administered (532 mg and 266 mg respectively). Reported fatal cases could indicate that liposome bupivacaine administration is not suitable for regional analgesia in high invasive surgical procedures, and that higher dose could be associated with higher risk of cardiotoxicity and neurotoxicity, and that dose reduction may be required in elderly and debilitated patients.

There is a trend towards an **increased rate of TESAEs** in Exparel group. Incidences of observed individual SAEs are low and additional analyses did not reveal new information. Nevertheless, there is a **clear dose related trend** for liposomal bupivacaine SAEs and it seems that there were more SAEs in **high invasive surgical procedures** (such as TKA and posterolateral thoracotomy).

Regarding **laboratory findings**, in depth assessment was provided in responses to the D120 LoQ, with revision of AEs listed in proposed PI. Following laboratory findings are included in proposed PI: hepatic enzyme increased, white blood cell count increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased.

There were considerably higher incidences of TEAEs and TESAEs **in elderly subjects** recorded. Although the TEAEs and SAEs incidences were higher for ≥ 65 years of age group, the applicant is of opinion that the greater sensitivity to bupivacaine cannot be ruled out, and that the higher prevalence of comorbidities and concomitant medications should be taken into account. It can be concurred that there is an increased risk of postoperative morbidity and mortality among elderly patients and that observed AE incidences are probably not only attributable to the concerned medicinal product. Moreover, similar AE incidences and similar differences between younger and older populations were observed in bupivacaine IR and placebo groups too.

Some specific AEs tend to increase by age (e.g. fall). As mentioned by the applicant, 'greater sensitivity of some older patients cannot be ruled out'. Given that motor dysfunction potentially leading to fall is one of characteristic AEs reported for Exparel, additional warning about increased risk to falls in elderly people have been included in the PI.

Comparison of race as intrinsic factor does not reveal remarkable differences taking into account that presented summary data in the submitted dossier are not easy to evaluate.

When evaluating the combined pool analysis, majority of subjects (1171/1645, 71.2% All Exparel, 497/625, 79.5% IR bupivacaine, 435/604, 72.0% placebo) had a baseline ASA class of 1-2. Although higher incidences of TEAE/TEAEs are expected in subjects with higher **ASA class 3-4**, there were a notably high number of individual AEs reported, except falls indicated by the applicant. Additional analysis confirmed that there were no meaningful differences when analysing Exparel doses and SOCs. No major differences among treatment groups were observed regarding incidences of TEAEs and TESAEs when analysed according to ASA status.

The applicant did not initially provide any discussion regarding **specific medical environment** (i.e. anaesthesia, concomitant rescue medications), neither possible clinically important considerations. In the following stages of the procedure the applicant provided satisfactory response regarding **drug**

interactions. The applicant has divided drug interactions in those related to bupivacaine in the systemic circulation and those interactions that impact the release characteristics of bupivacaine from Exparel. For drug interactions related to bupivacaine in the systemic circulation, information for bupivacaine HCl is adopted. This approach is acceptable. For drug interactions that impact the release characteristics of bupivacaine from Exparel *in vitro*, nonclinical and clinical physicochemical interaction studies were performed (please refer to PK assessment too). Admixing with either lidocaine, ropivacaine or mepivacaine has been shown to cause an immediate release of bupivacaine from DepoFoam. The applicant has conducted *in vitro* and nonclinical studies to evaluate interactions of Exparel with other commonly used products in the surgical setting (such as epinephrine, steroids, anti-infective drugs, opioids, and non-steroidal anti-inflammatory drugs) and has found that those products have minimal impact on the release of bupivacaine from Exparel. Minor discussion on neuromuscular blocking agents that can be expected to be administered concomitantly has been provided, stating that no impact of neuromuscular blocking agents with Exparel has been noted during the clinical trials. Although local anaesthetics can enhance the neuromuscular-blocking effect of neuromuscular blocking agents, this information is deemed as a common healthcare professionals' (dealing with local anaesthetics and neuromuscular blocking agents) knowledge and it is not necessary to be included in the PI. Co-administration with other local anaesthetics and their additive toxic effect. Information on use with other local anaesthetics or active substances structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine and mexiletine, because of additive systemic toxic effects has been added in the SmPC by the assessor.

Use in obstetrical paracervical block anaesthesia is contraindicated and there is recommendation against **use during pregnancy**. It is anticipated that clinicians are aware of increased issues of LAST in pregnant women, especially those at term, and no further warning is deemed necessary. Bupivacaine and its metabolite, pipercoloxylidide, are present in human milk at low levels. Because of the potential for serious adverse reactions in breastfed infants a decision must be made whether to discontinue **breast-feeding** or to discontinue/abstain from Exparel therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Information on **severe renal** and **severe hepatic impairment** have been substantiated in the responses to the D120 LoQ.

Overall, number of recorded **TEAEs leading to study discontinuation** is low. It is visible from the presented data that 266 mg and higher doses of liposome bupivacaine were associated with higher numbers of subjects with at least one TEAE leading to discontinuation of the study. It seems that all TEAEs leading to study discontinuation were recorded in regional analgesia pool.

Initially, the applicant failed to discuss and explore the **non-clinical findings** regarding **local tolerability** and to link them to clinical settings. They are particularly worrisome as they include subcutaneous mineralisation and irreversible granulomatous inflammation due to Depo Foam component. Moreover, presence of exogenous lipids seems to be a nidus for the development of foreign body type of reaction in surrounding tissues which is not reversible even after a period of one month. This was shown after a single application, but especially with repeat/prolonged exposure. It seems possible that prolonged or repeated application of Exparel could cause dystrophic changes at the injection site. The applicant addressed those issues in response to the D120 LoQ. It is recognised that Exparel material (exogenous lipids) can remain at the injection site for several weeks, and the normal clearance mechanisms for such material can result in local foreign body reactions, and the timeframe required for clearance can appear to cause a delay in recovery time dependent on the relative amount delivered and the site of administration. However, the clinical data show that non-clinical findings are not transferred to the clinical setting. **Wound healing issue** does not seem to be significant. Post-marketing data further strengthen this conclusion. It is expected to be monitored by routine pharmacovigilance activities.

The applicant has addressed the **post-marketing experience** according to the ICH M4E(R2) in responses to the D120 LoQ. Post-marketing data are presented for the period from 28 Oct 2011 to 27 Oct 2019. All the data are from the US. Estimated number of exposed subjects is high (357,452 patients treated for nerve block and 5,595,912 patients treated for infiltration). In the concerned period, there were 961 cases of ADRs reported, of those approximately 35% were serious ADR cases (339 serious cases) and 622 non-serious cases. During the same period, there were 1837 adverse events reported, including 611 serious and 1226 non-serious adverse events. 16 serious labelled drug-drug interaction medication errors were reported. The applicant has not identified any new safety issues from case reports. The applicant has identified 153 cases that are considered potential-LAST case reports and 19 fatal potential-LAST case reports in the above-mentioned post-marketing period. There is no particular signal and that routine pharmacovigilance measures should be employed.

Generally, the **PI data** have been adequately substantiated.

Of note, the applicant initially failed to address potential important safety issues as suggested through SAs given by various NCAs. MPA (2006) pointed out following potential issues:

- Safety of the product if unintentionally not handled correctly;
- Possibility of a very short time release of free bupivacaine in different clinical scenarios (e.g. sepsis, fever, acidosis);
- Safety of large doses of liposomal bupivacaine unintentionally injected intravenously;
- Safety of large doses of liposomal bupivacaine unintentionally injected intraarterially (e.g. in the neck region during interscalene block).

Sufficient data on above mentioned issues have been provided in response to the D120 LoQ and adequate information are proposed in the PI. The use of Exparel in different clinical scenarios (e.g. sepsis, fever, acidosis) still remains an uncertainty as the applicant has provided only quality data on this matter.

Intravascular and intra-articular routes of administration have been contraindicated.

Medical errors issue regarding undistinguishable appearance of Exparel and propofol, and one regarding additional use of local anaesthetics (only important potential risk outlined) are discussed in proposed RMP.

2.6.6. Conclusions on clinical safety

The CHMP was of the opinion that the available safety data supported the Application for Exparel. Though bupivacaine HCl has well known safety profile, this application concerns a drug that delivers active substance from liposomes, containing high dose of bupivacaine free base. This has been adequately reflected in the Product Information and Risk Management Plan.

2.7. Risk management plan

Safety concerns

Table 35: Summary table of safety concerns

Important identified risks	None
Important potential risks	Medication errors leading to systemic toxic reactions
Missing information	None

Pharmacovigilance plan

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary.

No additional pharmacovigilance activities are foreseen.

Risk minimisation measures

Table 36: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors leading to systemic toxic reactions	<p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> • SmPC Section 4.2 where there is guidance about the additive effects of local anaesthetics, not to use Exparel interchangeably with other bupivacaine formulations, and to administer Exparel by injection only • SmPC Section 4.3 where intravascular or intra-articular administration is contraindicated • SmPC Section 4.4 where there are warnings about concomitant use of local anaesthetics and not to substitute Exparel with other bupivacaine products • SmPC Section 4.5 where potential interactions with other medicinal products are described • SmPC Section 4.9 where overdose with Exparel and other local anaesthetics is described with treatment guidance • Package Leaflet Section 2 where there is guidance about other medicines and that the patient should NOT be given if Exparel is needed for injection into a blood vessel or artery • Restricted medical prescription • Single peel-off vial labels <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> • No additional risk minimisation measures 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

Based on the new formulation, the CHMP is of the opinion that a separate entry in the EURD list for Exparel liposomal is needed, as it cannot follow the already existing entry for bupivacaine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 28.10.2011. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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*.

2.9.2. 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:

Based on a detailed justification submitted by the applicant the QRD group decided to allow the use of minimum labelling particulars for the label of the 20 mL vial, mirroring the same minimum particulars as the ones included on the label of the 10 mL vial presentation. The Group also suggested to include the total content per total volume on the vials' labels.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". According to the Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011) pain can be described as acute or chronic according to its duration. Acute pain is considered adaptive, in that it has a warning function. It is of short duration

(generally up to a few weeks) and declines with the healing of the underlying injury or disease (e.g. post-surgical pain). Pain after surgery is a predictable part of the postoperative experience. However, like all pain, postoperative pain is complex and multidimensional. According to the applicant, three in four patients who experience acute postoperative pain report it as moderate, severe, or extreme in intensity. The current consensus clinical practice guidelines in Europe and the US recommend utilising multimodal analgesic regimens to manage acute postsurgical pain ([Chou 2016](#); [Meissner 2015](#); [European Society of Regional Anaesthesia & Pain Therapy 2019](#)). Multimodal analgesic regimens combine two or more agents or techniques that act by different analgesic mechanisms to provide enhanced pain relief.

Local anaesthetics are particularly useful for management of moderate-to-severe acute pain and have been shown to improve postsurgical analgesia. But their duration of effect is shorter than the duration of moderate-to-severe postsurgical pain. For example, IR bupivacaine has a labelled maximum duration of effect of eight hours for both field block and major nerve block ([Marcain SmPC](#)). According to the applicant Exparel was developed as a longer-acting analgesic that provides sustained relief from moderate-to-severe acute pain following surgery or traumatic injury.

3.1.2. Available therapies and unmet medical need

Multimodal analgesic regimens combine two or more agents or techniques that act by different analgesic mechanisms to provide enhanced pain relief while minimising the adverse side effects of any one agent.

The current treatment options for postsurgical analgesia include local anaesthetics, opioids, gabapentinoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. The selection of components of any pain management strategy are tailored to the patient, the surgical procedure, and the expected type, location, and duration of pain.

Local anaesthetics are particularly useful for management of moderate-to-severe acute pain and have been shown to improve postsurgical analgesia and reduce opioid utilisation. Local anaesthetics may be used as a field block to create local analgesia around an injury, surgical site, or tissue plane or as a peripheral nerve block to create regional analgesia around a larger area. While conventional local anaesthetics are commonly used because of their long-standing benefit-risk profile, their duration of effect is typically shorter than the duration of moderate-to-severe postsurgical pain, which can often extend for several days. For example, IR bupivacaine has a labelled maximum duration of effect of eight hours for both field block and major nerve block.

3.1.3. Main clinical studies

The applicant provides efficacy results from the 6 Phase 2, randomised, double-blind, multicentre, dose finding/ranging studies and 12 Phase 3, randomised, double-blind, multicentre studies which are grouped by the intended effect of Exparel to produce local analgesia or regional analgesia:

- Local analgesia (field block) studies: 201 and 207 (hernia repair); 209, 312, and 316 (haemorrhoidectomy); 208, 311, and 331 (TKA); 317 (bunionectomy); 210 (breast augmentation); 329 (third molar extraction); and 411 (Caesarean section).
- Regional analgesia (peripheral nerve block) studies: 203 (bunionectomy); 323 and 326 (TKA); 327 (TSA/RCR); and 322 (thoracotomy).

For local analgesia

There were five Phase 2 studies and seven Phase 3 studies. The Phase 2 studies evaluated Exparel doses ranging from 66 mg to 532 mg and were used to inform dosing for the Phase 3 studies. The Phase 3 studies assessed the efficacy and safety of Exparel doses ranging from 106 mg to 532 mg.

For regional analgesia

Exparel was administered as a peripheral nerve block. There were two Phase 2 studies and four Phase 3 studies. The Phase 2 studies evaluated Exparel doses ranging from 67 mg to 310 mg and were used to inform the dosing for the Phase 3 studies. The Phase 3 studies assessed the efficacy and safety of Exparel 133- and 266-mg doses.

The surgical procedures selected for the clinical studies are representative of surgeries that would be expected to lead to moderate-to-severe pain of sufficient duration to benefit from a long acting local anaesthetic and where sustained management of acute pain is traditionally managed with a CPNB or opioids. The surgical procedures included models of both somatic pain (e.g., third molar extraction, bunionectomy, major orthopaedic surgery) as well as models of mixed somatic/visceral pain (e.g., abdominal/thoracic surgery).

Different doses were evaluated and compared with saline placebo and IR bupivacaine (as standard of care).

3.2. Favourable effects

- Exparel 266 mg was superior to placebo in the management of postoperative pain for 72 hours in haemorrhoidectomy (AUC₀₋₇₂ of the NRS-R pain intensity scores using wWOCF for rescue medications and LOCF for missing data in an appropriate efficacy population); Study **316**.
- Statistically significant reduction in secondary outcomes regarding opioids (total opioid use through 72 hours, opioid-free through 72 hours and time to first opioid) were observed in Study **316**.
- Exparel 106 mg was superior to placebo in the management of postoperative pain for 24 hours in bunionectomy (AUC₀₋₂₄ of the NRS-R using wWOCF for rescue medications and LOCF for missing data in an appropriate efficacy population); Study **317**.
- Statistically significant reduction in secondary outcomes regarding opioids (number of Percocet tablets through 24 hours, rescue-free through 24 hours and time to first Percocet) were observed in Study **317**.
- Sensitivity analysis in study **317** (wWOCF+mWOCF; wWOCF on Completers and LOCF) were supportive of the primary analysis.
- Exparel 266 mg + bupivacaine 89 mg was superior to bupivacaine 89 mg in the management of postoperative pain during 12-48 hours postoperatively in total knee arthroplasty (AUC₁₂₋₄₈ of the VAS pain intensity scores using wWOCF for rescue medications and MI for missing data in an appropriate efficacy population); Study **331**.
- Statistically significant reduction in secondary outcomes regarding opioids (total opioid use through 48 hours, opioid-free through 48 hours and time to first opioid) were observed in Study **331**.
- Statistically significant reduction in one of several secondary outcomes regarding opioids (total opioid through 72 hours) was observed in Study **411**.
- Exparel 266 was superior to placebo in the management of postoperative pain for 72 hours in total knee arthroplasty (AUC₀₋₇₂ of the NRS-R using wWOCF for rescue medications and LOCF for missing data in an appropriate efficacy population); Study **323**.
- Statistically significant reduction in one of several secondary outcomes regarding opioids (total opioid through 72 hours) was observed in Study **323**.

- Exparel 133 mg was superior to placebo in the management of postoperative pain for 48 hours in Total Shoulder Arthroplasty or Rotator Cuff Repair (AUC₀₋₄₈ of the VAS pain intensity score using wWOCF+MI in an appropriate efficacy population); Study **327**.
- Statistically significant reduction in secondary outcomes regarding opioids (total opioid use through 48 hours, opioid-free through 48 hours and time to first opioid) were observed in Study **327**.
- Rescue medications were mainly comparable across phase 3 studies, although some differences exist.

3.3. Uncertainties and limitations about favourable effects

- Superiority of Exparel over primary or secondary outcomes was not established for 3 studies in local analgesia setting (**311**, **312** and **329**) and 2 studies in regional analgesia setting (**322** and **326**).
- The definition of the primary efficacy population in Study **411** is not in line with the ITT principle. When all randomised and treated patients were analysed, the difference in total opioid use through 72 hours (primary endpoint) in Exparel vs comparator groups was no longer statistically significant. Results for the primary outcome for the re-analyses show a LS mean treatment difference of -2.9 MME with a wide 95% CI that crosses zero (95% CI -15.4 to 9.6) and a p-value of 0.33. No significance was observed in any of the other outcomes when the results were re-analysed, except for the secondary outcome of pain intensity scores that met the criteria for non-inferiority (consistent with the primary analysis).
- Exparel 266 mg + bupivacaine 44 mg was non-inferior to bupivacaine 44 mg during 72 hours in Caesarean section (AUC₀₋₇₂ of the VAS pain intensity score using wWOCF+MI in an inadequately defined efficacy population); Study **411**.
- A statistically significant difference regarding the percentage in opioid-free subjects through 72 hours and time to first opioid was not observed between groups (Exparel 266 mg + bupivacaine 44 mg vs bupivacaine 44 mg) in Study **411**.
- A statistically significant difference regarding the percentage in opioid-free subjects through 72 hours and time to first opioid was not observed between groups (Exparel 266 mg vs placebo) in Study **323**.
- Based on Phase 2 studies no clear dose-effect pattern was obvious.
- Harder to treat patients were excluded from every study.
- About 33% of patients were from Europe, the rest were from the US. According to provided literature data, European patients have statistically significant lower pain scores in the first day after orthopaedic surgery and use less opioids.
- Active comparators in studies 331 and 411 are sub-dosed.
- Baseline pain medications were not standardised across main phase 3 studies – each study had a different protocol regarding baseline pain management. Some didn't allow for baseline pain medications.
- Imputation procedures for rescue pain medication and missing data varied across studies. The amount of missing data in Study **331** was substantial. In the primary evaluation period (from 12 to 48 hours), the proportion of missing pain intensity scores was between 11.6% and 52.9% in Exparel+IR bupivacaine group and between 8.7% to 42% in IR bupivacaine group. An

imbalance in the amount of missing data between treatment arms is noted and the nature of missing data is unknown (wasn't recorded).

- In study **316** lack of a statistically significant difference concerning PONV-free time, use of antiemetics and postoperative constipation was observed despite a significant reduction in the use of opioids in Exparel arm.
- In study **316**, when wWOCF for rescue pain medication is not applied, the difference in primary outcome did not reach statistical significance.
- Clinical significance of the results is inconsistent across primary and key secondary outcomes in the studies that reached statistical significance.
- Only 2 phase 3 studies showed a statistically significant difference in the percentage of opioid-free subjects at 72 hours in favour of Exparel.
- In the majority of main Phase 3 studies all or nearly all patients required opioid rescue through 72 hours.
- Out of initially opioid-free patients, more of them allocated to Exparel required an opioid at later timepoints compared to those allocated to the comparator. This was observed in Study 411, where additional 11 patients (15.3%) who were opioid-free through 72 hours in Exparel+IR bupivacaine group required an opioid from 72 hours to 14 days, while in IR bupivacaine group additional 5 patients (7.1%) required opioids. The same pattern is observed in Study 317, where additional 5 patients (5.1%) who were rescue-free at 24 hours in Exparel group required an opioid from 24-72 hours, while in placebo group no additional patients required rescue medications from 24-72 hours. The same pattern is observed in Study 327, where additional 12 patients (17.4%) who were opioid-free through 24 hours in Exparel group required an opioid from 24-72 hours, while in placebo group no additional patients required opioids from 24-72 hours.

3.4. Unfavourable effects

Percentages of subjects with at least one TEAE was high among the all doses liposome bupivacaine but did not differ substantially from bupivacaine HCl and placebo groups (around 72%). Higher percentages of AEs were assessed as related in all doses liposome bupivacaine group in comparison to bupivacaine HCl and/or placebo pertaining to particular SOCs (cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, investigations, nervous system disorders). Cardiac and nervous system disorders pronouncedly differ from bupivacaine HCl and/or placebo (cardiac disorders - 0.8 vs 0.2 vs 0; nervous system disorders - 8.7 vs 1.3 vs 8.6). Higher incidences of liposome bupivacaine SAEs belonging to particular SOCs (cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, nervous system disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders) when comparing to bupivacaine HCl and/or placebo.

266 mg and higher doses of Exparel were associated with higher numbers of subjects with at least one TESAE and severe TEAE, higher numbers of subjects with at least one TEAE leading to discontinuation of the study and death. Clear dose related trend for liposomal bupivacaine SAEs and ones exclusively reported for liposome bupivacaine was observed.

Most commonly reported TEAEs in combined pool: nausea (33.3%), constipation (16.2%), vomiting (13.4%), pyrexia (11.7%) and pruritus (7.5%).

Common AEs were reported with higher frequencies for liposome bupivacaine *compared to placebo*: nausea, constipation, anaemia, oedema peripheral, tachycardia, muscle spasms, anaemia postoperative, back pain, hypoesthesia, chills, oropharyngeal pain, pain in extremity, dysuria.

Common AEs were reported with higher frequencies for liposome bupivacaine *compared to bupivacaine HCl*: vomiting, hypoesthesia oral, dysgeusia, dizziness, motor dysfunction, muscle twitching, confusional state, hyperhidrosis, pruritus generalised, dyspepsia, muscle contractions involuntary, haemoglobin decreased, post procedural oedema, hepatic enzyme increased, dry mouth.

Common AEs were reported with higher frequencies for liposome bupivacaine *compared both to bupivacaine HCl and placebo*: pyrexia, anxiety, somnolence, bradycardia, erythema, hyponatraemia, lethargy and blood glucose increased.

Safety data presented represent more serious safety profile in regional analgesia setting. In regional analgesia pool AEs were reported with higher frequencies for liposome bupivacaine compared both to bupivacaine HCl and placebo (belonging to cardiac disorders, nervous system disorders, infectious, injuries, post procedural complications, hepatic disorders). All TEAEs leading to study discontinuation were recorded in regional analgesia pool. The applicant identified specific issues related to regional analgesia. Almost all reported falls are attributable to regional analgesia setting in TKA.

Fatal cases occurred in 2 studies: study 208 (TKA, Phase 2, Local analgesia pool) and study 322 (posterolateral thoracotomy, Phase 3, Regional analgesia pool). 3 were reported in Exparel group, 1 in IR bupivacaine group and 4 in placebo group. Study investigators considered all 8 fatal cases not related to the study drug. In all three fatal cases in Exparel groups, higher doses were administered (532 mg and 266 mg respectively). Cases from study 322 were reported in elderly male patients and, among other reported fatal AEs, common one was coded as cardiac arrest.

The recommendation to avoid using another bupivacaine (according to US label expanded to **all** local anaesthetic) 96 hours after using Exparel limits analgesic options in case of failure of Exparel and circumstances where revision or reoperation is needed.

There was significant difference in incidences of TEAEs and SAEs in elderly population, aged ≥ 65 years in comparison to < 65 years of age population. Proposed PI was amended to properly reflect differences in safety profile in elderly when compared to patients < 65 years. Although the incidences were higher for ≥ 65 years of age group, the greater sensitivity to bupivacaine cannot be ruled out, and the higher prevalence of comorbidities and concomitant medications should be taken into account. Observed AE incidences are probably not only attributable to the concerned medicinal product. Moreover, similar AE incidences and similar differences between younger and older populations were observed in bupivacaine IR and placebo groups too. There were higher incidences of TEAEs and TESAEs in subjects in the ASA class 3-4 groups as compared with those in the ASA class 1-2 groups in Exparel groups. There were no meaningful differences when analysing Exparel doses and SOC.

Medical errors issue regarding undistinguishable appearance of Exparel and propofol. Important potential risk identified in the proposed RMP: medication errors due to additional use of local anaesthetics.

Submitted post-marketing data include most commonly reported ADRs: "Injury, Poisoning, and Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy, pain), Skin And Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest)." 35% of all post-marketing cases were serious. The applicant has identified 153 cases that are considered potential-LAST case reports and 19 fatal potential-LAST case reports in the above-mentioned post-marketing period.

3.5. Uncertainties and limitations about unfavourable effects

Number of important issues initially were not addressed by the applicant or were not detailed enough, and they raise important uncertainties and limitations about knowledge of safety profile:

Potential drug-drug interactions with medicinal products excluded during clinical development.

Profound applicability to the EU population.

According to quality data there seems not to be a specific safety issue due to possibility of a very short time release of free bupivacaine in different clinical scenarios (e.g. sepsis, fever, acidosis), although real clinical settings might bring additional risks. Those specific clinical scenarios remain uncertainty.

Toxicity and overdose potential exist since large doses of liposome bupivacaine and other local anaesthetics can be administered by both surgeon and anaesthesiologist during same surgical procedure.

3.6. Effects Table

Table 37

Effect	Short Description	Unit	Exparel	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
<i>Local Analgesia</i>						
AUC0-72 of the NRS-R (primary outcome)	Area under the curve of NRS-R pain intensity scores through 72 hours	AUC; LS Mean (SE)	141.8 (10.7)	202.5 (10.7)	<i>Strengths:</i> statistically significant results for primary and all key opioid-related outcomes <i>Uncertainties:</i> clinical relevance of the primary outcome questionable; time-averaged difference in pain intensity scores is <1; sensitivity analyses (when wWOCF for rescue medications not applied) failed to show statistical significance for the primary outcome; lack of statistically significant difference concerning incidence of pre-defined opioid-related adverse events; difference in consumption of opioids is driven by the difference in the first 24 hours	316
		Difference in LS mean Exparel vs placebo (95% CI)	-60.7 (-90.4, -31.0)			
AUC0-24 of the NRS-R (primary outcome)	Area under the curve of NRS-R pain intensity scores through 24 hours	AUC; LS Mean (SE)	123.9 (4.49)	146.2 (4.59)	<i>Strengths:</i> statistically significant results for primary and all key opioid-related outcomes <i>Uncertainties:</i> clinical relevance of the primary outcome questionable; time-averaged difference in pain intensity scores is <1; secondary outcomes related to opioids are not clinically relevant when absolute figures are analysed; additional 5 patients (5.1%) who were rescue-free at 24 hours in Exparel group required an opioid rescue from 24-72 hours (compared to none in placebo group)	317
		Difference in LS mean Exparel vs placebo (95% CI)	-22.3 (-34.8, -9.8)			
<i>Regional Analgesia</i>						

Effect	Short Description	Unit	Exparel	Placebo	Uncertainties/ Strength of evidence	References
AUC0-72 of the NRS-R (primary outcome)	Area under the curve of NRS-R pain intensity scores through 72 hours	AUC; LS Mean (SE) Difference in LS mean Exparel vs placebo (95% CI)	418.9 (16.86)	515.5 (16.95)	<i>Strengths:</i> time-averaged difference in pain intensity scores 1.3 points over 72 hours; total amount of opioids significantly lower in Exparel group <i>Uncertainties:</i> the difference in opioid consumption is driven by the first 24-48 hours; other opioid-related secondary outcomes (opioid-free and time to first opioid) failed to show statistical significance	323
AUC0-48 of the VAS (primary outcome)	Area under the curve (AUC) of the VAS pain intensity scores through 48 hours	AUC; LS Mean (SE) Difference in LS mean Exparel vs placebo (95% CI)	136.4 (12.09)	254.12 (11.77)	<i>Strengths:</i> time-averaged difference in pain intensity scores 2.5 points over 48 hours; statistically significant results for primary and all key opioid-related outcomes <i>Uncertainties:</i> additional 12 patients (17.4%) who were opioid-free through 24 hours in Exparel group required an opioid from 24-72 hours (compared to none in placebo group)	327
				-117.7 (-150.9, -84.5)		
Unfavourable Effects						
Nausea	Most commonly reported TEAE in the combined pool (all Exparel doses)	%	33.3	30.8	higher incidence of TEAEs and TESAEs in elderly subjects	Combined pool (all Exparel doses)
Cardiac and nervous system disorders	related TEAEs by SOCs in the combined pool (all Exparel doses)	%	6.8 25.1	5.0 (IR bupivacaine) 14.9 (IR bupivacaine)	inferior safety profile in the regional analgesia comparison to local analgesia setting	Combined pool (all Exparel doses)
Falls	Adverse event specific to Regional analgesia	%	2.2	0.3	almost all reported falls are attributable to regional analgesia setting in TKA	Regional Analgesia pool (all doses)
LAST	LAST cases from post-marketing experience in the US (28 Oct 2011 to 27 Oct 2019)	Number of cases	153 potential-LAST case reports and 19 fatal potential-LAST cases		In the concerned period, there were 961 cases of ADRs reported, of those approximately 35% were serious ADR cases	D120 responses

3.7. Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Exparel has shown superiority over placebo in the management of postoperative pain in several surgery models (bunionectomy, haemorrhoidectomy, total knee arthroplasty and total shoulder arthroplasty or rotator cuff repair).

Exparel showed an 18% increase in the proportion of opioid-free subjects 72 hours in Study 316. These patients were able to remain completely free of opioids, which is the ultimate goal. Another benefit is reduction in total postoperative opioid use, which was observed in Study 316 through 72 hours (46% relative reduction), in Study 323 through 72 hours (26.3% relative reduction) and Study 327 through 48 hours (77.2% relative reduction). The expected time to onset of analgesia with Exparel is 2 minutes. The duration of analgesic efficacy as shown in pivotal phase 3 trials was 24 hours in local analgesia studies and between 24 hours and 72 hours in regional analgesia studies.

The safety profile is acceptable and adequately reflected in Product Information and Risk Management Plan.

3.8. Balance of benefits and risks

The benefits observed in the pivotal clinical trials are considered to outweigh the risks.

3.9. Conclusions

The overall B/R of Exparel indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults is considered positive.

4. Recommendations

Outcome

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

Exparel liposomal is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults (see section 5.1)

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Not applicable

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

Not applicable