30 April 2020
EMA/302500/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Suboxone

International non-proprietary name: buprenorphine / naloxone

Procedure No. EMEA/H/C/000697/X/0042

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AR	Assessment report
ASMF	Active Substance Master File
AUC	Area under the concentration-time curve
BE	Bioequivalence
BNX	Buprenorphine / Naloxone
CEP	Certificate of Suitability of the European Pharmacopoeia
CI	Confidence interval
Cmax	Maximum plasma concentration
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
COWS	Clinical Opiate Withdrawal Scale
CSR	Clinical study report
EEA	European economic area
EU	European Union
FTIR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
HDPP	High density polypropylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low-Density Polyethylene
LoQ	List of questions
MAA	Marketing Authorisation Application
MO	Major objection
MS	Mass Spectrometry
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
OUD	Opioid use disorder
PDE	Permitted daily exposure
PEO	Polyethylene oxide
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
Resp.	Or
QbD	Quality by design
SAE	Serious adverse event
SL	Sublingual
SmPC	Summary of Product Characteristics
TDD	Total daily dose
TEAE	Treatment emergent adverse event
Tmax	Time to maximum plasma concentration
UDS	Urine drug screen
USP	United States Pharmacopoeia
UV	Ultra violet

1. Background information on the procedure

1.1. Submission of the dossier

Indivior Europe Limited submitted on 8 March 2019 extensions of the marketing authorisation.

The MAH applied for an extension to introduce a new pharmaceutical form (sublingual film) associated with four new strengths (2/0.5, 4/1, 8/2, and 16/4 mg) and a new route of administration (either sublingual or buccal administration)

The MAH applied for the following indication for Suboxone:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 (2) points (c) (d) (e) - Extensions of marketing authorisations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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 MAH did not seek Scientific advice at the CHMP.

The Applicant sought scientific advice within the scope of the preceding line extension procedure EMEA/H/C/697/X/10 in Germany in November 2009. After the preceding MAA was withdrawn, a Pre-submission Meeting was held in Germany in October 2018 to discuss the data package for the newly submitted line extension procedure EMEA/H/C/697/X/0042.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	8 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 July 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	2 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 June 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	27 February 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	30 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
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 Suboxone on	30 April 2020

2. Scientific discussion

2.1. Problem statement

Suboxone sublingual (SL) film (buprenorphine/naloxone film), the subject of this application, is a fixed-dose sublingual film containing buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 (ratio of the bases). The sublingual film dosage form is intended to be an additional formulation of buprenorphine/naloxone as found in Suboxone SL tablet for the treatment of opioid dependence. The Applicant intends to submit a line extension to Suboxone SL tablet as addition of a new pharmaceutical form.

The Applicant has developed the soluble film technology as a means of improving compliance and reducing the potential for diversion and misuse. Suboxone SL film is intended for use in the treatment of opioid dependence over the same buprenorphine/naloxone dose range of 2 mg/0.5mg to 24 mg/6mg as Suboxone SL tablets.

Approval history

Suboxone SL film 2 mg/0.5 mg and 8 mg/2 mg dose strengths were first approved in the United States (US) in August 2010, and subsequently in Australia (February 2011) and Malaysia (July 2013). The 4 mg/1 mg and 12 mg/3 mg dose strengths were first approved in the US in August 2012 and subsequently in Australia (May 2014).

Suboxone SL tablets, containing buprenorphine and naloxone in a 4:1 ratio of the bases, are marketed in the European Economic Area (EEA) as Suboxone 2/0.5 mg, 8/2 mg, and 16/4 mg buprenorphine + naloxone, respectively.

Suboxone SL film has been developed at dose strengths of 2/0.5 mg, 4/1 mg, 8/2 mg, and 12/3 mg buprenorphine plus naloxone as fixed combination.

The addition of naloxone to Suboxone formulations is to deter parenteral misuse as it is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine or methadone.

It is noted that parts of the clinical dossier have already been evaluated within the scope of preceding line extension procedure EMEA/H/C/697/X/10 (concerning the 2/0.5 mg and 8/2 mg dose strengths), which could not be positively finalised. The Applicant decided to withdraw the MAA after receipt of the D120 LoQ, since it was considered that the MOs on pharmaceutical quality could not be addressed within the given timeframe.

Contrary to preceding line extension procedure EMEA/H/C/697/X/10, which was confined to the sublingual method of administration, the present MAA refers to both the sublingual and buccal administration.

2.1.1. Disease or condition

Indication

Suboxone SL film has the same indication as the currently approved Suboxone SL tablet product, i.e., substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Suboxone is indicated in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

Opioid dependence remains a major risk factor for ill health and death. It can result in a range of problems for the users and their family and friends, as well as for the wider community. These problems include health and social costs (to both the individual and the community), including the risk of overdose, spread of diseases and family breakdown; health costs; economic costs associated with morbidity, mortality and absenteeism related to illicit drug use; and the cost of law enforcement for drug-related crime. A key aim of opioid dependence treatment programs is to bring individuals into a comprehensive treatment environment where medical, social and psychological issues are addressed in addition to treating individuals' dependence on heroin or other opioids. Another key aim is to stop individuals from injecting drugs to aid in reducing the spread of HIV and hepatitis.

2.1.2 Management

The buprenorphine-containing products Suboxone and Subutex have made a valuable contribution to the treatment of opioid dependence. Buprenorphine reduces both the craving for opioids and the severity of the opioid withdrawal syndrome. However, due to its opioid properties buprenorphine has the potential to be diverted for misuse by various routes, including by intravenous (IV) injection. Diversion for misuse by IV injection is one of the main identified risks of buprenorphine treatment for opioid dependence and it is discussed in detail in the Risk Management Plan submitted with this application. Naloxone has been added to buprenorphine in both Suboxone tablets and Suboxone films to reduce the risk of diversion for intravenous use.

Buprenorphine is an opioid with partial agonistic properties at the mu-opioid receptor and antagonistic properties at the kappa-opioid receptor. It dissociates slowly from mu-opioid receptors. It has been shown to be an effective treatment for opioid dependence, including maintenance and detoxification, when used within a framework of medical, social and psychological treatment.

Naloxone is a potent antagonist at mu-opioid receptors and produces signs and symptoms of opioid withdrawal in individuals physically dependent on full opioid agonists when administered parenterally.

The addition of naloxone to Suboxone formulations is to deter parenteral misuse as it is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine or methadone.

Suboxone SL film was developed as a pharmacotherapy for opioid dependence. The film formulation provides an alternative dosage form to Suboxone SL tablets. It was developed with the intention of producing similar efficacy and safety to Suboxone SL tablets, but with additional safety and compliance features. In particular, the formulation was created for the purpose of reducing the risk of diversion for illicit use, reducing unintended and potentially dangerous exposure in children, and improving compliance to treatment.

When placed in the sublingual cavity and exposed to contact with saliva, the film is expected to instantly adhere to the mucosa, which is supposed to make it difficult to remove for subsequent illicit use. If a relevant advantage in terms of adherence resp. removability could be shown for the films (as compared to the tablets), this would be an important consideration in supervised dosing environments.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as orange sublingual films containing the active substances buprenorphine hydrochloride and naloxone hydrochloride dihydrate, in four strengths: 2 mg / 0.5 mg, 4 mg / 1.0 mg, 8 mg / 2 mg, 12 mg / 3 mg.

Other ingredients are: Polyethylene oxide, Maltitol liquid, Natural lime flavour, Hypromellose, Citric acid, Acesulfame potassium, Sodium Citrate, Sunset yellow (E110), White ink.

The product is available in blister packages as described in section 6.5 of the SmPC.

The finished product Suboxone sublingual film is a line extension to the existing centralised marketing authorisation for Suboxone sublingual tablets.

2.2.2. Active Substance - Buprenorphine hydrochloride

The active substance suppliers of buprenorphine hydrochloride are identical to those already authorised for Suboxone sublingual tablets. The structure and content of the following active substance assessment is based on the already approved Suboxone sublingual tablet marketing authorisation, with relevant updated information included.

General information

The chemical name of buprenorphine hydrochloride is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride corresponding to the molecular formula $C_{29}H_{41}NO_4HCl$. It has a relative molecular mass of 504.1 g/mol and the following structure:

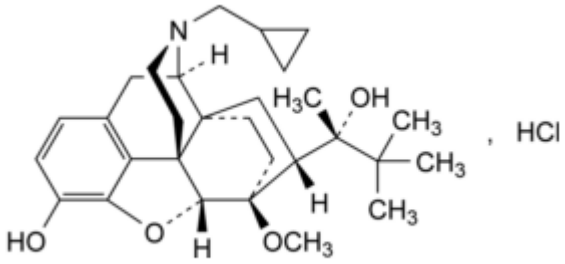


Figure 1: active substance structure

Buprenorphine hydrochloride is a white or almost white, crystalline powder that is sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 %) and practically insoluble in cyclohexane. The chemical structure of Buprenorphine hydrochloride was elucidated by a combination of elemental analysis, spectroscopic analyses (UV, IR, 1H-NMR and MS), and single crystal analysis by X-ray diffraction.

Manufacture, characterisation and process controls

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

Buprenorphine hydrochloride is synthesized in seven main steps using well defined starting materials with acceptable specifications.

There have been some minor updates to the in-process controls that are applied during the synthesis, which overall are deemed adequate. The specifications and control methods for intermediate products, starting materials and reagents, yields of steps and material quantities have been presented and satisfactorily updated as needed.

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. Additional impurities not mentioned in Ph. Eur. monograph have been evaluated in silico using two complementary (Q)SAR methodologies (DEREK and Leadscope) and demonstrated to not have any mutagenic potential.

The risk assessments on the active substance Buprenorphine HCl performed by the suppliers, were conducted in line with the requirements of documents EMA/189634/2019 and CMDh/404/2019 and EMA/428592/2019 published respectively on EMA website and CMDh website.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program and is identical to that authorised for Suboxone sublingual tablets.

The active substance is packaged in (LDPE) polythene bags inside propylene (HDPP) kegs with screw caps which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (NIR, FTIR, Chlorides), appearance of a 2% w/v methanolic solution (Ph. Eur.), acidity or alkalinity (Ph. Eur.), specific optical rotation (USP), assay (USP/titration), related substances (HPLC), loss on drying (Ph. Eur.), water (KF), residue on ignition (USP), residual dichloromethane (GC) and particle size (laser diffraction).

The active substance complies with the Ph. Eur. monograph for buprenorphine hydrochloride, with additional tests (in-house and USP) also described. The analytical methods used are those described in the official Ph. Eur. monograph except for alternative methods for identity (NIR), specific optical rotation (USP) and determination of related substances (HPLC). In the updated specification the particle size is controlled using a laser diffraction method and appropriate limits have been set for D90, D50 and D10.

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

Updated batch analysis data from 3 recent batches of the active substance are provided. The results are within the updated specifications and consistent from batch to batch.

Stability

Stability data from nine batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market, for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines, were provided.

The stability results indicate that buprenorphine hydrochloride manufactured by the proposed supplier remains physically and chemically stable for 3 years at long-term and intermediate conditions. The stability results justify the proposed retest period of 12 months in the proposed container.

2.2.3. Active substance - Naloxone hydrochloride dihydrate

General information

The chemical name of Naloxone hydrochloride dihydrate is 4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate corresponding to the molecular formula C19H22ClNO4,2H2O. It has a relative molecular mass of 399.9 g/mol and the following structure:

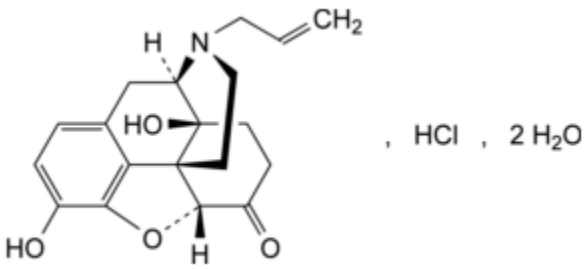


Figure 2: active substance structure

As there is a monograph of Naloxone hydrochloride dihydrate in the European Pharmacopoeia, the manufacturers of the active substance have been granted a Certificates of Suitability of the European Pharmacopoeia (CEP) for Naloxone hydrochloride dihydrate which has been provided within the current Line Extension Application.

Certificate of suitability No.: R1-CEP 2006-261-Rev 03 (CEP Holder: MacFarlan Smith Limited)

Certificate of suitability No.: R0-CEP 2009-294-Rev 00 (CEP Holder: SpecGx LLC)

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The risk assessments on the active substance Naloxone HCl dihydrate, performed by the suppliers, were conducted in line with the requirements of documents EMA/189634/2019 and CMDh/404/2019 and EMA/428592/2019 published respectively on EMA website and CMDh website.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), specific optical rotation (USP), loss on drying (USP), chloride content (USP), appearance of solution (Ph. Eur.), acidity or alkalinity (Ph. Eur.) related substances (Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Ph. Eur., USP) and residual solvents (USP).

The specifications are in line with the monograph and Certificates of Suitability of the European Pharmacopoeia. Additional specifications have been set for loss on drying and identification by IR in line with USP. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

CEP Holder: MacFarlan Smith Limited (R1-CEP 2006-261-Rev 03):

The re-test period defined in the CEP is 2 years if stored at a temperature not exceeding 25°C in polyethylene bag placed in either a polypropylene or aluminum or polyethylene container.

CEP Holder: SpecGx LLC (R0-CEP 2009-294-Rev 00):

No re-test period is mentioned on the CEP.

Stability data from 20 batches of active substance from the proposed manufacturer stored in various container closure systems representative of that intended for the market, for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The parameters evaluated during these stability studies were appearance, loss on drying, assay (titration method), assay (HPLC), related substances (known, unknown, total; HPLC-method).

The stability results indicate that the active substance manufactured by this supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with no special storage conditions in the proposed container.

2.2.4. Finished Medicinal Product

Description of the product and Pharmaceutical development

Suboxone sublingual film is a fixed dose combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate at a ratio of 4:1 (ratio of the bases), identical to the ratio of active substances presented in the already authorised Suboxone sublingual tablets. The qualitative composition of the finished product is presented in Table 3.

The sublingual films are available in four strengths, two low strength formulations (2 mg / 0.5 mg and 4 mg / 1 mg) and two high strength formulations (8 mg / 2 mg and 12 mg / 3 mg). They are supplied individually sealed in aluminium foil pouches

Table 1: qualitative composition of finished product

Name of Ingredient	Function	Reference to Standards
Active Ingredient(s)		
Buprenorphine HCl	Active ingredient	In-House [a]
Naloxone HCl Dihydrate	Active ingredient	In-House [a]
Other Ingredients		
Acesulfame Potassium	Sweetener	Ph. Eur., USP
Citric Acid, Anhydrous	Buffer	Ph. Eur., USP, JP
Maltitol solution (Lycasin 80/55)	Filler/wetting agent/sweetener	NF
Hypromellose (Methocel E5 LV)	Film former/strengthener	Ph. Eur., USP, JP
Hypromellose (Methocel E15 LV)	Film former/strengthener	Ph. Eur., USP, JP
Polyethylene Oxide [b] (WSR-N10 PEO-LEO)	Film former/flexibility	Ph. Eur., NF
Polyethylene Oxide [b] (WSR-N80 PEO-LEO)	Film former/flexibility	Ph. Eur., NF
Polyethylene Oxide [b] (WSR-1105 PEO-LEO)	Film former/mucoadhesive	Ph. Eur., NF
Sodium Citrate, Anhydrous	Buffer	USP
Natural Lime Flavour 3000180	Flavour	In-House
Sunset Yellow (E110) (FD&C Yellow No. 6)	Colour	In-House
White Ink	Print ink	In-House

Any processing aids or solvents which are driven off during manufacture are not included in the table above. These components are listed in 3.2.P.3.2.
[a] In-house specifications comply with USP/Ph. Eur. and include additional controls.
[b] Polyethylene oxide complies with Ph. Eur. requirements for high molecular mass macrogols.

Suboxone sublingual film has been developed to offer an alternative form of transmucosal buprenorphine/naloxone treatment to patients with opioid drug dependence. While clinically and therapeutically equivalent to Suboxone sublingual tablet, Suboxone sublingual film offers the advantages of sticking to the mucosal surface more vigorously, ensuring optimal treatment effect and inhibiting the ease of removal for non-compliance, diversion or misuse.

Key components of the formulation are a combination of water-soluble film forming polymers, sweeteners and flavouring agents (to mask the bitter taste of the buprenorphine HCl), colorant and buffer. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, or other relevant acceptable standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Extensive pharmaceutical development data, partly applying QbD principles, was provided. The objective of formulation development was to develop a film with the same buprenorphine: naloxone ratio as present in suboxone sublingual tablets. Aim of early development was to obtain film strips of appropriate physical quality offering the required tensile strength and tear resistance while exhibiting sufficient tackiness and pliability for use. Formulation development was driven by a pilot PK study. During pharmaceutical

development, specific tests were conducted to be able to better describe the physical properties of the film strips. Relevant physico-chemical properties of the active ingredients were addressed appropriately.

During the procedure, the development of the *in-vitro* dissolution test, its discriminatory power and the appropriateness of the proposed limits were discussed in detail. Following extensive discussion during the procedure, the dissolution specification was tightened for both active substances. The discriminatory properties of the dissolution method have been demonstrated. The submitted data sufficiently confirm that the proposed method conditions are appropriate to fulfil Ph. Eur. chapter 2.9.3 requirements.

The manufacturing sites involved in the development of the product were presented. QbD principles were used in the development of the finished products and their manufacturing process however, no design spaces were claimed for the manufacturing process of the finished products. Individual process steps with potential impact on the critical quality attributes were subject to risk assessment and acceptable measures were taken to minimize the risks identified.

The primary packaging is child-resistant individual sachets consisting of four composite layers of polyethylene terephthalate (PET), Low Density Polyethylene (LDPE), aluminium foil and Low-Density Polyethylene (LDPE), which are heat sealed at the edges. 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. Suitability of the material as to protect from humidity, light and microbiological ingress is inferred from the results of the stability studies. Child-resistance has been demonstrated in line with EU requirements.

Manufacture of the product and process controls

The manufacturing process consists of four main steps:

- Dispensing of raw materials,
- Mixing (preparation of the bulk dispersion of the active pharmaceutical ingredients dispersed homogenously in a solution of the excipients),
- Coating and drying (coating of the bulk dispersion onto a substrate, followed by drying to bulk film),
- Cutting and pouching (cutting the bulk film roll into individual strips and creation of the final unit dose (cutting and sealing in pouches).

Stages 1, 3 and 4 are identical for Suboxonone sublingual film strengths.

The manufacturing process is considered to be a non-standard process.

The in-process controls are adequate for this type of manufacturing process / pharmaceutical form. Information on validated holding and processing times was provided.

Major steps of the manufacturing process have been validated by a number of studies. 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 release specifications include appropriate tests for this kind of dosage form; appearance, identification (HPLC, UV), Buprenorphine assay (HPLC-UV), Naloxone assay (HPLC-UV), Buprenorphine related

substances (HPLC-UV), Naloxone related substances (HPLC-UV), dissolution (HPLC-UV), moisture (titrimetric), content uniformity (USP) and microbial limits (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing. The proposed acceptance criteria for related substances are derived from profound knowledge of the degradation kinetics and pathways of the active ingredients. All specified impurities which exceed the ICH Q3B(R2) qualification limit were qualified in line with ICH M7 (R1).

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. Batch analysis data on three batches using a validated ICP-MS 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.

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.

Batch analysis results are provided for 8 commercial scale batches (380 kg) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 18 batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing, manufactured at commercial scale, covering all proposed strengths and packed in the primary packaging proposed for marketing.

Photostability studies were not conducted due to the protective properties of the primary packaging material which is acceptable.

The batches were tested against the proposed specifications. All results met the acceptance criteria for shelf life. No other significant changes have been observed. The final shelf-life and storage conditions have been set to ensure acceptable stability.

Stability data on the proposed holding time of the bulk film were provided.

The applicant provided a commitment to conduct additional transit stability studies covering the updated specification and methods and completing real time studies following the short-term excursions, to be initiated upon the finalisation of the specification and methods upon completion of this line extension.

Based on available stability data, the proposed shelf-life of 18 months when stored below 25 °C in the proposed container closure system, as stated in the SmPC (section 6.3), is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. Materials of animal and/or human origin are not used in the manufacturing process for the finished products sublingual film and do not come into

direct contact with the finished product. TSE/BSE statements are provided throughout the module 3 for the active pharmaceutical ingredient, excipients, packaging materials, manufacturing process and finished product, to demonstrate as such.

2.2.5. 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.

2.2.6. 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. Data has been presented to give reassurance on viral/TSE safety.

2.2.7. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The registered marketed tablet product has established the overall basis for the nonclinical safety for the drug substances and the drug product.

Aspects on development
Nonclinical data concerning general pharmacology, pharmacokinetics and toxicology of the active substances buprenorphine and naloxone in support of the SUBOXONE sublingual film is considered by the Applicant to be identical to that previously evaluated for the SUBOXONE sublingual tablet and was therefore not re-submitted with this application.
Instead, the nonclinical information presented in this application includes aspects related to

- the change in dosage form, for example, potential abuse of the film product,
- the potential toxicity of naloxone- as well as buprenorphine-related impurities in the film formulation.

Additionally, a search of the scientific literature published from 01 January 2012 to 01 October 2018 was conducted in the Medline database to find relevant new non-clinical information concerning buprenorphine and naloxone. The literature was reviewed, and relevant articles obtained to identify new information that addresses the nonclinical toxicity of the active pharmaceutical ingredients buprenorphine and naloxone. Copies of the cited literature are included as part of this submission.

The Applicant has provided a Nonclinical Overview that has been written by Julie Tripp (MS, CVT, DABT), Preclinical Toxicologist, Indivior Inc, domiciled in Fort Collins, USA. Report is dated February 7, 2019 and makes reference to 35 publications up to year 2018.

GLP aspects
The single and repeat dose toxicity studies as well as the genotoxicity studies (with one exception) and the toxicokinetic study submitted with this application were conducted according to GLP requirements.

2.3.2. Pharmacology

No new proprietary data.

2.3.3. Pharmacokinetics

The results of the toxicokinetic evaluation to support a 28-day repeat dose toxicity study in dogs were provided (see section 2.3.4).

28-Day Repeated-dose Toxicity Study of Aged SUBOXONE Sublingual Film Product

Type of Study	Species and Strain	Method of Admin	Duration of Dosing	Doses (mg/kg)	GLP	Testing Facility	Study Number
Repeated -Dose Toxicity	Dog, Beagle	Oral, sublingual	28 days	Buprenorphine: 4.8 mg/kg Naloxone: 12 mg/kg	Yes	MPI Research, 54943 North Main Street, Mattawan, Michigan 49071, USA	INLS-C106-16

No other new pharmacokinetic data were provided.

2.3.4. Toxicology

Scope of the nonclinical toxicology program
With regard to the active substances buprenorphine and naloxone, the nonclinical safety data in support of the SUBOXONE sublingual film formulation is considered by the Applicant to be identical to that previously evaluated for the SUBOXONE sublingual tablet formulation and was therefore not re-submitted with this application.

Instead, the nonclinical toxicology program focused on aspects which could be potentially related to the change in dosage form (i.e. sublingual film versus sublingual tablet), specifically:

- Acute and repeat dose toxicity following potential IV abuse of the film product
  (Studies 516690, 516706, 310564, 311531, 787634)
- The potential toxicity of naloxone- as well as buprenorphine-related impurities contained in the film formulation
  (Studies RC010106, RC010107, INL-C106-16, RC010110, RC010111, RC010112, RBRS-V001-00-12)

Overall, the nonclinical toxicity program for SUBOXONE sublingual film comprised the studies shown in the following Table:

Table: Nonclinical toxicity program conducted for SUBOXONE sublingual film

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number
Single-Dose Toxicity	Rat, Sprague Dawley	Intravenous, subcutaneous	1 day	Intravenous 1 mL/kg Subcutaneous 0.5 mL/kg	Yes	Charles River, Edinburgh, UK	516690
Repeat-Dose Toxicity	Rat, Sprague Dawley	Intravenous	14 days	1 mL/kg	Yes	Charles River, Edinburgh, UK	516706
	Rat, Alpk:APfSD (Wistar-derived)	Oral, by food	7 days	2000 ppm (0.2% in diet)	Yes	Central Toxicology Laboratory Macclesfield, UK	RC010106
	Rat, Alpk:APfSD (Wistar-derived)	Oral, by food	28 days	2000 ppm (0.2% in diet)	Yes	Central Toxicology Laboratory Macclesfield, UK	RC010107
	Dog, Beagle	Oral, sublingual	28 days	Buprenorphine: 4.8 mg/kg Naloxone: 1.2 mg/kg	Yes	MPI, Mattawan, MI, USA	INLS-C106-16

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number
Genotoxicity	S. typhimurium TA98, TA100, TA1535, TA1537 *E. coli* WP2P, WP2P *uvrA*	*In vitro* (co-incubation)	3-day co-incubation period	Buprenorphine: 50 to 2000 µg/plate	Yes	Central Toxicology Laboratory Macclesfield, UK	RC010110
	Human lymphocytes	*In vitro* (co-incubation)	3-hour (with S9 mix) and 3-hour or 20-hour (without S9 mix) co-incubation period)	Suboxone Tablet extract: 20 to 520 µg/mL	Yes	Central Toxicology Laboratory Macclesfield, UK	RC010111
	Rat, Alpk:APfSD	Oral (by gavage)	Animal sacrifice 4 days after oral application	Buprenorphine: 500, 1000 and 2000 mg/kg	Yes	Central Toxicology Laboratory Macclesfield, UK	RC010112

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number
	S. typhimurium TA98, TA100, TA1535, TA1537 *E. coli* WP2P, WP2P *uvrA*	*In vitro* (co-incubation)	3-day co-incubation period	Buprenorphine: naloxone mix (4:1): 50 to 2500 µg/plate	Yes	Central Toxicology Laboratory Macclesfield, UK	RC980112
	Human TK6 cell lines GenM-C01 and GenM-T01	*In vitro* (co-incubation) for up to 48 hours	Co-incubation for up to 48 h	D09EJ Film: 0.98 to 250 µg/mL in DMSO 0.04 to 10 mg/mL in sterile water	No	BioReliance, Rockville, MD, USA	RBRS-V001-00-12
Carcinogenicity	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Reproductive and Developmental Toxicity	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Local Tolerance	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Other Toxicity Studies	Rat, Sprague Dawley (whole blood), *in vitro*	Co-incubation	1-hour co-incubation period	150 µL of test item solution in 2.85 mL of whole blood	Yes	Charles River, Edinburgh, UK	310564

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance	Testing Facility	Study Number
	Human (adult volunteers who claim to be drug-free for 5 days; whole blood), *in vitro*	Co-incubation	1-hour co-incubation period	150 µL of test item solution in 2.85 mL of whole blood	Yes	Charles River, Edinburgh, UK	311531
	Rat Wistar, (sodium heparine plasma) Human (healthy adult volunteers) (sodium heparine plasma), *in vitro*	Co-incubation	N/A (immediate assessment of drug precipitation after mixing)	0, 0.2, 0.4, 0.6, 0.8 and 1.0 mL of test item solution (to give with rat or human plasma 2 mL total volume)	No	Charles River, Edinburgh, UK	787634

Toxicokinetics

Type of Study	Species and Strain	Method of Admin	Duration of Dosing	Doses (mg/kg)	GLP	Testing Facility	Study Number
Repeated -Dose Toxicity	Dog, Beagle	Oral, sublingual	28 days	Buprenorphine: 4.8 mg/kg Naloxone: 12 mg/kg	Yes	MPI Research, 54943 North Main Street, Mattawan, Michigan 49071, USA	INLS-C106-16

Acute and repeat dose toxicity

A number of studies were conducted in order to evaluate the potential effects of IV abuse of SUBOXONE sublingual film as compared with SUBOXONE sublingual tablets.

Comparative data were generated for both the approved SUBOXONE sublingual tablet and for SUBOXONE sublingual film

Prior to *in vivo* testing in rats, both SUBOXONE test formulations were investigated *ex vivo* in both human and rat whole blood to ensure absence of test substance-induced haemolysis. In addition, different ratios of SUBOXONE test items/plasma and solvents used for test item dissolution were tested *ex vivo* for compatibility, i.e. absence of test item precipitation (see 2.3.4, Other toxicity studies, Other studies).

Following a pilot, single dose IV and SC toxicity study in rats (study 516690), a repeat dose toxicity study in rats (study 516706) was conducted to compare the toxicity profiles of SUBOXONE sublingual tablets (8 mg/2 mg) and SUBOXONE sublingual film (8 mg/2 mg) following 14 consecutive days of IV administration.

- The results of the single dose IV and SC toxicity study and of the 14-day repeat dose IV toxicity study in rats show that parenteral application of extracts of SUBOXONE sublingual film at a dose which can be expected to correspond respectively exceed a human equivalent dose (HED) anticipated for the human IV abuse situation, did not result in acute life-threatening toxicity.
- There was no indication that IV abuse of SUBOXONE sublingual film at the doses evaluated carried a higher risk than would be anticipated following abuse of the equivalent dose of SUBOXONE sublingual tablet.
- Behavioural effects, lower kidney and liver weights and higher thymus weights were noted in the 14-day toxicity study in both treated groups compared with the controls, however, without associated histopathological changes. Since a recovery period was not included, it remains unclear whether these effects are reversible.

Genotoxicity

In a bacterial reverse mutation (AMES) test, a buprenorphine-naloxone-mixture (4:1 ratio as in SUBOXONE sublingual film) was negative, indicating the absence of a mutagenic potential of the active substances buprenorphine and naloxone.

The genotoxic potential of buprenorphine- and naloxone-related impurities was evaluated (see 2.3.4 Other toxicity studies, Studies on Impurities).

Carcinogenicity

No new data provided.

Reproductive and developmental toxicity

No new proprietary data provided.

Local tolerance

Separate studies were not conducted. However, information on local tolerance of SUBOXONE sublingual film can be derived from the 28-day sublingual toxicity study in dogs (INLS-C106-16) and from the clinical studies conducted.

Other toxicity studies

Studies on impurities

Buprenorphine-related impurities

Toxicological characterization of buprenorphine-related impurities exceeding the qualification limit defined in ICH Q3B(R2) in a GLP-compliant 7-day palatability study (Study RC010106) and a subsequent GLP-compliant 28-day dietary toxicity study (Study RC010107) both in Alpk:APfSD (Wistar-derived) rats, and in 3 genotoxicity studies, using a bacterial reverse mutation (AMES) test (Study RC010110), an *in vitro* cytogenetic test for chromosomal aberrations in peripheral blood lymphocytes (Study RC010111) and a rat bone marrow micronucleus test (Study RC010112), was performed using an extract derived from SUBOXONE sublingual tablets instead of SUBOXONE film strips.

Naloxone-related impurities

Evaluation of the mutagenic potential of naloxone-related impurities was performed in accordance with ICH M7(R1) by using two different QSAR methodologies [knowledge-based (DEREK) and statistically-based (Leadscope)]. According to the *in silico* evaluation, none of the 17 naloxone-related impurities identified in SUBOXONE sublingual film is considered to have a mutagenic potential.

For toxicological qualification of naloxone-related impurities exceeding the qualification limit according to ICH 3B(R2), a threshold level of 50 µg/day was used. However, for the final product specification tighter limits for identification (0.25%, corresponding to 15 µg TDI per impurity) and qualification (0.625%, corresponding to 37.5 µg TDI per impurity) were implemented.

In a 28-day repeated-dose sublingual toxicity study in male and female Beagle dogs (Study INLS-C106-16), conducted with 3 differently aged preparations of SUBOXONE sublingual film with the aim to provide toxicological qualification for the contained naloxone-related impurities, all 3 preparations resulted in a prolongation of the QTc-interval at study day 1 (by 14.35%, 13.48% and 15.22%, respectively) but not at study day 28. One group of animals exhibited a greater array of clinical observations, which included findings of leaning, panting, skin warm to touch, watery faeces, limb function impaired (hind limbs), lateral recumbency and stereotypy and which were not noted in the two other groups. This group also had higher incidence rate of decreased activity and vomitus/emesis.

Other studies

IV injection of extracts of SUBOXONE sublingual tablet or SUBOXONE sublingual film has the potential to result in precipitation of the test items in plasma at 37°C. A procedure described by Portmann and Simmonds (1995) was used to investigate this possibility (Study 787634). The data suggest that rat plasma is potentially more sensitive than human plasma in this respect. The results permitted calculation of a nonprecipitating IV dose for use in rat toxicology studies and provided some assurance that precipitation of the test items in plasma was unlikely to be of clinical importance following IV abuse in man.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment can stop in Phase I. Naloxone and buprenorphine hydrochloride PEC surfacewater values are below the action limit of 0.01 µg/L and both active substances are not a PBT substance as log Kow does not exceed 4.5.

Therefore, naloxone and buprenorphine hydrochloride are not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

With regard to the results of the performed literature search (see CTD 2.6.6 Toxicology Written Summary, section 10), an expert statement was provided by the Applicant, that, on basis of the retrieved references, an update of the SUBOXONE sublingual film product information (in particular of SmPC section 5.3) is not necessary.

Acute and repeat dose toxicity

A number of studies were conducted in order to evaluate the potential effects of IV abuse of SUBOXONE sublingual film as compared with SUBOXONE sublingual tablets.

- The results of the single dose IV and SC toxicity study and of the 14-day repeat dose IV toxicity study in rats show that parenteral application of extracts of SUBOXONE sublingual film at a dose

which can be expected to correspond respectively exceed the HED anticipated for the human IV abuse situation, did not result in acute life-threatening toxicity.
- There was no indication that IV abuse of extracts of SUBOXONE sublingual film at the doses evaluated carried a higher risk than would be anticipated following abuse of the equivalent dose of SUBOXONE sublingual tablet.
- Behavioural effects, lower kidney and liver weights and higher thymus weights were noted in the 14-day toxicity study in both treated groups compared with the controls, however, without associated histopathological changes. Since a recovery period was not included, it remains unclear whether these effects are reversible.

In addition, an 28-day sublingual toxicity study with aged SUBOXONE sublingual film charges was conducted in dogs (Study INLS-C106-16, see below , Other toxicity studies, Studies on impurities.

Genotoxicity

In a bacterial reverse mutation (AMES) test, a buprenorphine-naloxone-mixture (4:1 ratio as in SUBOXONE sublingual film) was negative, indicating the absence of a mutagenic potential of the active substances buprenorphine and naloxone.

The genotoxic potential of buprenorphine- and naloxone-related impurities was evaluated (see below, Other toxicity studies, Studies on impurities).

Local tolerance

Separate studies were not conducted. However, information on local tolerance of SUBOXONE sublingual film can be derived from the 28-day sublingual toxicity study in dogs (INLS-C106-16) and from the clinical studies conducted. In view of these data, the local tolerance of the Suboxone film formulation is considered sufficiently characterized and, although some minor adverse local reactions were observed, does not give cause for significant concern.

Other toxicity studies

Studies on impurities

Buprenorphine-related impurities

Evaluation of the mutagenic potential of buprenorphine-related impurities: According to an *in silico* evaluation performed in accordance with ICH M7(R1) by using two different QSAR methodologies, none of the buprenorphine-related impurities identified in SUBOXONE sublingual film is considered to have a mutagenic potential.

Further studies using a bacterial reverse mutation (AMES) test (Study RC010110), an *in vitro* cytogenetic test for chromosomal aberrations in peripheral blood lymphocytes (Study RC010111) and a rat bone marrow micronucleus test (Study RC010112) are not considered to provide additional relevant regulatory information, since the concentrations of the buprenorphine-related impurities used in these studies were too low to allow for definite conclusions.

Toxicological characterization of the single buprenorphine-related impurity exceeding the qualification limit defined in ICH Q3B(R2) was

- considered qualified by virtue of being a major metabolite of buprenorphine.

Additional data: A GLP-compliant 7-day palatability study (Study RC010106) and a subsequent GLP-compliant 28-day dietary toxicity study (Study RC010107) were performed in rats using an extract derived from SUBOXONE sublingual tablets (the Applicant has provided evidence that buprenorphine-related

impurities present in the film strips are comparable in qualitative and quantitative terms to those present in the sublingual tablets).

Naloxone-related impurities
Evaluation of the mutagenic potential of naloxone-related impurities: According to an *in silico* evaluation performed in accordance with ICH M7(R1) by using two different QSAR methodologies, none of the 17 naloxone-related impurities identified in SUBOXONE sublingual film is considered to have a mutagenic potential.

Toxicological qualification of naloxone-related impurities exceeding the qualification limit (NMT 0.5%) according to ICH 3B(R2) were toxicologically qualified.

Additional data: A 28-day repeated-dose sublingual toxicity study in male and female Beagle dogs (Study INLS-C106-16), with a daily dose of about 4.8 mg/kg buprenorphine and 1.2 mg/kg naloxone, was conducted with 3 differently aged preparations of SUBOXONE sublingual film with the aim to provide additional toxicological reassurance concerning the safety of charges stored for up to 30 months at 25/30°C and 60/65% relative humidity:
Toxicokinetics: The C_{max} and AUC-values measured showed that the animals had been adequately exposed to buprenorphine and its main metabolite norbuprenorphine.
Observations: In general, observations and effects were typical of expected pharmacologic effects of a high dosage of buprenorphine and were primarily noted only in the first 2 weeks of the 4 week study. All animals survived to the scheduled necropsy. Numerical differences in clinical observations may reflect individual differences in sensitivity to effects of buprenorphine/naloxone in the low number (3 per sex) study groups. A prolongation of the QT_c-interval was observed on study day 1 but not on study day 28. The Applicant has provided nonclinical and clinical evidence that effects observed on day 1 are not related to direct effects on the hERG channel current (the Applicant considers an indirect effect via an influence on autonomic tone) and are not clinically relevant. No other unexpected effects were observed.

Other studies

The absence of significant *ex vivo* haemolysis indicated that the proposed dose solutions could be safely administered IV and SC in rat toxicology studies and the data indicating a similar absence of *ex vivo* haemolysis in human whole blood also provide some assurance that clinically important haemolysis is unlikely to result from IV abuse.

IV injection of extracts of SUBOXONE sublingual tablet or SUBOXONE sublingual film has the potential to result in precipitation of the test items in plasma at 37°C. A procedure described by Portmann and Simmonds (1995) was used to investigate this possibility (Study 787634) using human plasma and Wistar rat plasma. The obtained data suggest that rat plasma is potentially more sensitive than human plasma as a model to detect precipitation of IV applied SUBOXOXE sublingual film extracts in plasma.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers all non-clinical issues to be resolved. From the non-clinical point of view, marketing authorisation may be granted.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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.

- Tabular overview of clinical studies

A number of Phase I PK studies were conducted to evaluate PK parameters, bioavailability, and dose proportionality of Suboxone SL film. This application focuses on the 12 Phase I studies (4 pilot studies, 6 comparative bioequivalence (BE) studies and 2 dose proportionality studies) that are relevant to the evaluation of Suboxone SL film.

Table Overview of Completed Comparative PK and dose proportionality studies with SUBOXONE SL film

Study no.	Study type	Route of administration	SUBOXONE film dose strength used	Total dose administered
20-250-SA	Bioequivalence	Sublingual / buccal	2 mg/0.5 mg	2 mg/0.5 mg
20-272-SA	Bioequivalence	Sublingual / buccal	2 mg/0.5 mg (2 strips)	4 mg/1 mg
20-273-SA	Bioequivalence	Sublingual / buccal	8 mg/2 mg	8 mg/2 mg
1003395	Bioequivalence	Sublingual / buccal	2 mg/0.5 mg (2 strips) 8 mg/2 mg (1 strip)	12 mg/ 3mg
20-B20-AU	Bioequivalence	Sublingual / buccal	12 mg/3 mg	12 mg/3 mg
20-A90-AU*	Bioequivalence	Sublingual / buccal	16 mg/4 mg	16 mg/4 mg
20-291-SA	Dose proportionality	Sublingual	2 mg/0.5 mg 2 mg/0.5 mg (2 strips) 8 mg/2 mg 12 mg/3 mg 16 mg/4 mg	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg 16 mg/4 mg
20-293-SA	Dose proportionality	Buccal	2 mg/0.5 mg 2 mg/0.5 mg (2 strips) 8 mg/2 mg 12 mg/3 mg 16 mg/4 mg	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg 16 mg/4 mg

*This study has been discussed in the context of safety only.

See Module 2.7.1, Table 10 for further details regarding these studies.

During the development of Suboxone SL film, 4 pilot bioequivalence studies (20-197-SA, 20-A70-AU, 20-A71-AU and 20-A72-AU) were conducted to determine the most appropriate formulation and to compare the film to Suboxone SL tablets. The results of the pilot studies are summarized in Mod. 2.7.1 (p.73f). Full CSRs were provided in Mod. 5. Given the availability of six BE studies (five of these declared as pivotal) plus two dose proportionality studies that were conducted with the final film formulation, the pilot studies are not further discussed within the scope of the present MAA.

BE study 20-A90-AU concerns the 16/4 mg film formulation dose strength, which is not subject of the present MAA. Data obtained from study 20-A90-AU will therefore only be included in the safety section of the present overview.

Two patient studies were conducted to evaluate the safety of Suboxone SL film when used to induct and maintain patients with OUD.

Study No.	**Study type**	**Population**	**Route of administration**	**Suboxone film dose strength used**
RB-US-07-0001	Phase II, open label, safety / local tolerability, 12-wk treatment with films	N=382 Opioid dependent patients in 3 US centres	Sublingual / buccal	2/0.5 mg, 8/2 mg, 12/3 mg, 16/4 mg
RB-US-07-0002	Phase II, db, induction of OUD patients onto buprenorphine resp. bupren./nalox. over 5 days, primary efficacy: COWS	N=34 OUD patients in 1 US center	Sublingual	2/0.5 mg bupren./nalox, 8/2 mg bupren./nalox

2.4.2. Pharmacokinetics

The comparison between the SL tablets and films after SD administration is based upon the following five BE studies:

20-250-SA	1 x 2/0.5 mg SL film vs SL tablets vs buccal film
20-272-SA	4/1 mg, administered as 2 x 2/0.5 mg SL film vs SL tablets vs buccal film
20-273-SA	1 x 8/2 mg SL film vs SL tablets vs buccal film
10003395	12/3 mg, administered as 1 x 8/2 plus 2 x 2/0.5 mg SL film vs SL tablets vs buccal film

20-B20-AU	1 x 12/3 mg SL film vs 1 x 12/3 mg buccal film vs 1 x 8/2 plus 2 x 2/0.5 mg SL tablet

It is noted that 4/5 of the BE studies above (all studies apart from 20-B20-AU) were previously evaluated within the scope of preceding line extension procedure EMEA/H/C/697/X/10, which could not be positively finalised. The Applicant decided to withdraw the MAA after receipt of the D120 LoQ, since it was considered that the MOs on pharmaceutical quality could not be addressed within the given timeframe.

Contrary to preceding line extension procedure EMEA/H/C/697/X/10, which was confined to the sublingual method of administration, the present MAA refers to both the sublingual and buccal administration.

Methods

As concerns the method of administration, the subject's mouth is wetted and rinsed by 30 ml of water before administration. The corresponding dosing recommendation is also given in the proposed package leaflet "*Drink water to moisten your mouth first.*"

After dissolution of the sublingually / buccally placed treatment 240 ml of water were administered. The chosen method of administration is acceptable as a standardised procedure within the scope of bioequivalence studies for these types of dosage forms.

All studies were conducted in opioid-naive and/or nondependent healthy volunteers under a naltrexone block in order to improve the tolerability of the study drugs.

The chosen sampling period of 144 h was largely sufficient as demonstrated by the fact that the plasma concentration curve asymptotically approaches the x-axis from about 24 hours onwards.

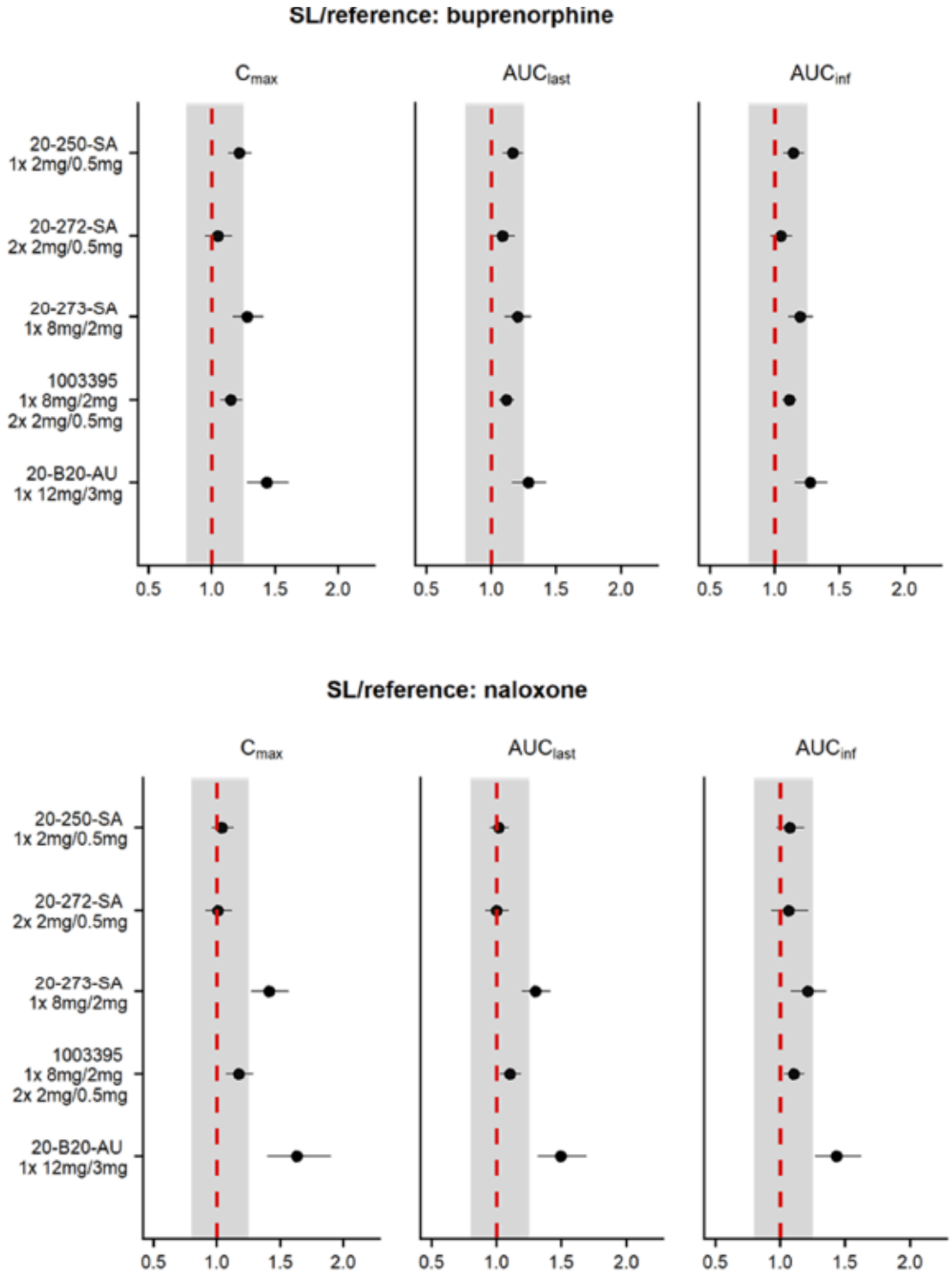
Dosing days were separated by a washout period of at least 14 days for the BE and dose proportionality studies.

The respective bioanalytical reports and validation reports were provided. Long-term stabilities of all methods for buprenorphine, norbuprenorphine and naloxone in human plasma were shown to cover the period of study sample storage (for summary, please refer to Table 2, Mod. 2.7.1). The results of Incurred Sample Reanalysis demonstrate reproducibility of sample analysis. Overall, description of analytical method and associated method validation are acceptable.

- ***Results of the five SD BE studies***

Results across the five pivotal bioequivalence studies are summarized in the Figures below for buprenorphine and naloxone, respectively. Across the bioequivalence studies, plasma exposures to buprenorphine and naloxone after SL or buccal administration of Suboxone SL film were comparable in most cases to that observed after SL administration of Suboxone SL tablets, although technically not bioequivalent at all dosage strengths.

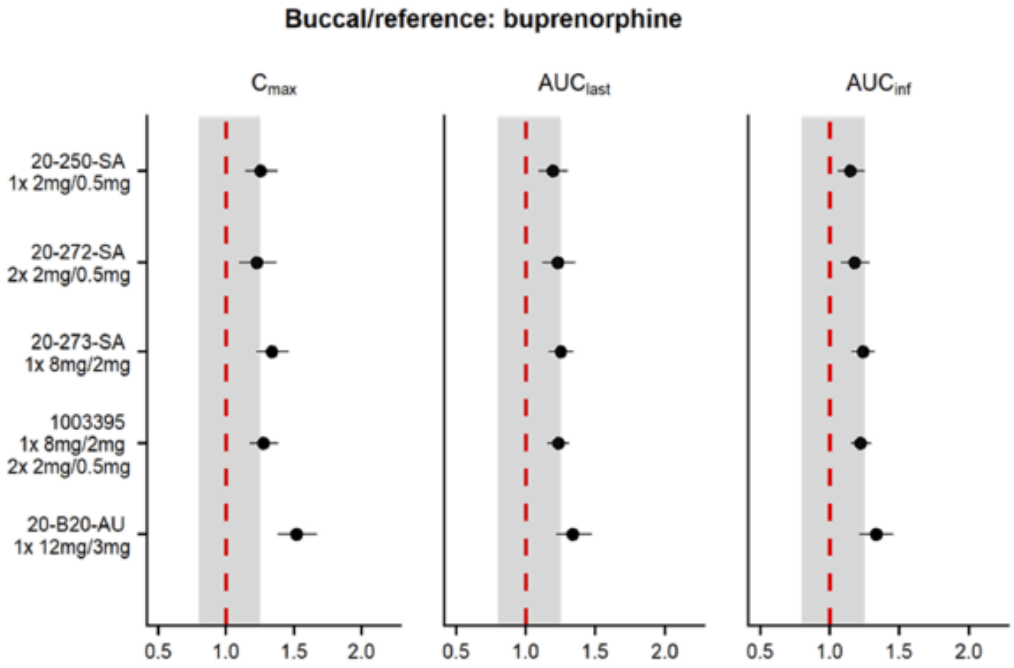
Geometric Mean Ratio (90% CI) of PK parameters Following SL Administration of Buprenorphine/Naloxone SL Film vs. Reference Tablets Across Studies

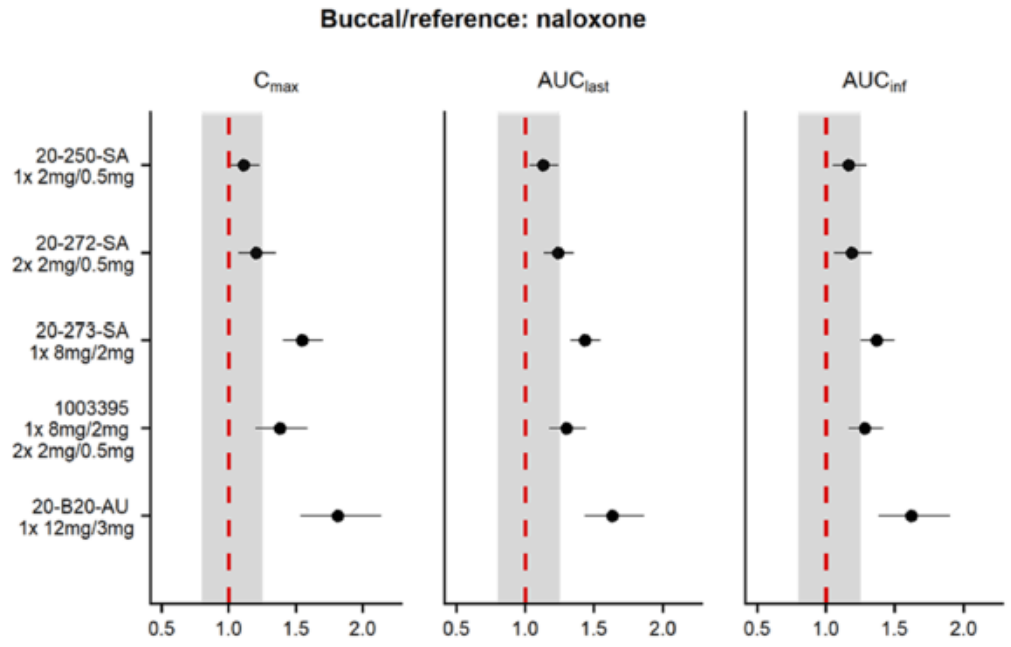


The vertical red dashed line indicates a ratio of 1; Gray shaded area=0.80 to 1.25 bioequivalence range Data derived from Studies 20-250-SA (Tables 11.4.3.7, 11.4.3.13), 20-272-SA (Tables 11.4.3.7, 11.4.3.15), 20-

273-SA (Tables 11.4.3.7, 11.4.3.9), 1003395 (Tables 11.4.3.7, 11.4.3.9) and 20-B20-AU (Tables 11.4.3.7, 11.4.3.17)

Geometric Mean Ratio (90% CI) of PK Parameters Following Buccal Administration of Buprenorphine / Naloxone SL Film vs. Reference Tablets Across Studies





The vertical red dashed line indicates a ratio of 1; Gray shaded area=0.80 to 1.25 bioequivalence range Data derived from Studies 20-250-SA (Tables 11.4.3.8, 11.4.3.14), 20-272-SA (Tables 11.4.3.8, 11.4.3.16), 20-273-SA (Tables 11.4.3.10, 11.4.3.12), 1003395 (Tables 11.4.3.10, 11.4.3.12) and 20-B20-AU (Tables 11.4.3.9, 11.4.3.19)

Influence of food

The influence of food has not been examined for the new formulation. Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and gluco-conjugation in the small intestine and the liver. Both for the SL tablets and the SL film strips the largest portion of buprenorphine is absorbed transmucosally, i.e. is not influenced by any food ingestion. In line with the Suboxone SL tablets' SmPC, it is recommended that patients should not swallow or consume food or drink until the film is completely dissolved.

- ***Dose proportionality - Sublingual***

Study 20-291-SA

Dose proportionality study to compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buprenorphine/naloxone film strip (sublingual) investigational formulations as single doses, manufactured by MonoSol Rx, LLC for Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.

Table Pharmacokinetic Parameters of Buprenorphine

	Treatment A (2/0.5 mg)				Treatment B (4/1 mg)				Treatment C (8/2 mg)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	31	1.54	0.68	44.33	31	1.48	0.57	38.16	31	1.40	0.45	32.38
C_{max} (ng/mL)	31	1.07	0.525	49.26	31	1.66	0.794	47.81	31	3.55	1.23	34.71
AUC_{last} (hr*ng/mL)	31	7.178	2.836	39.50	31	13.42	6.133	45.70	31	28.71	8.826	30.74
AUC_{inf} (hr*ng/mL)	28	8.434	3.207	38.02	31	14.62	6.446	44.09	31	30.66	9.241	30.14
AUC_{Extrap} (%)	28	12.97	5.27	40.64	31	8.96	3.76	41.97	31	6.57	4.04	61.50
λ_z (hr^{-1})	28	0.0444	0.0394	88.77	31	0.0426	0.0607	142.53	31	0.0229	0.0101	44.22
$T_{1/2}$ (hr)	28	22.71	13.01	57.29	31	25.67	13.30	51.80	31	36.55	16.38	44.82
T_{last} (hr)	31	49.94	18.36	36.76	31	72.26	30.71	42.50	31	110.71	33.18	29.97
C_{last} (ng/mL)	31	0.0347	0.00827	23.83	31	0.0333	0.00720	21.59	31	0.0358	0.0101	28.16

	Treatment D (12/3 mg)				Treatment E (16/4 mg)			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	30	1.43	0.53	36.96	31	1.29	0.37	28.81
C_{max} (ng/mL)	30	4.80	2.14	44.64	31	6.05	2.42	39.93
AUC_{last} (hr*ng/mL)	30	39.86	14.71	36.90	31	50.32	16.38	32.55
AUC_{inf} (hr*ng/mL)	30	41.74	15.08	36.13	31	53.40	18.58	34.79
AUC_{Extrap} (%)	30	4.91	2.34	47.64	31	5.27	4.70	89.15
λ_z (hr^{-1})	30	0.0208	0.0060	29.04	31	0.0196	0.0066	33.70
$T_{1/2}$ (hr)	30	36.07	10.48	29.06	31	40.37	17.22	42.66
T_{last} (hr)	30	122.40	24.69	20.17	31	129.29	20.25	15.66
C_{last} (ng/mL)	30	0.0353	0.00966	27.39	31	0.0444	0.0288	64.97

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.16, 14.2.17, 14.2.19, 14.2.21, and 14.2.23

Exposure to buprenorphine increased with dose of buprenorphine in the film strips. In general, peak exposure to buprenorphine was observed at approximately 1.5 hours and mean estimates of Cmax ranged from 1.07 ± 0.525 ng/mL after 2/0.5 mg to 6.05 ± 2.42 ng/mL after 16/4 mg. Likewise, overall systemic exposure, based on AUC values, increased with dose. Mean estimates of AUClast ranged from 7.178 ± 2.836 hr*ng/mL after 2/0.5 mg to 50.32 ± 16.38 after 16/4 mg.

Table Pharmacokinetic Parameters of Naloxone

Parameter	Treatment A (2/0.5 mg)				Treatment B (4/1 mg)				Treatment C (8/2 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	30	0.73	0.19	26.16	30	0.74	0.18	24.20	30	0.79	0.23	28.83
C_{max} (pg/mL)	30	48.5	25.9	53.44	30	72.8	33.7	46.36	30	193	84.6	43.86
AUC_{last} (hr*pg/mL)	30	100.6	41.30	41.05	30	164.1	68.02	41.45	30	442.9	134.4	30.34
AUC_{inf} (hr*pg/mL)	30	105.1	41.08	39.10	30	171.0	69.53	40.66	30	454.8	135.0	29.68
AUC_{Extrap} (%)	30	5.33	4.52	84.72	30	4.41	3.90	88.38	30	2.78	1.81	65.25
λ_z (hr^{-1})	30	0.4203	0.1716	40.83	30	0.3894	0.1341	34.45	30	0.2411	0.1798	74.57
$T_{1/2}$ (hr)	30	2.01	1.03	51.12	30	2.18	1.53	70.22	30	5.15	3.66	71.04
T_{last} (hr)	30	9.47	3.75	39.60	30	10.53	3.75	35.59	30	18.93	7.79	41.12
C_{last} (pg/mL)	30	1.59	0.453	28.44	30	2.61	3.96	151.37	30	1.89	1.08	57.29

Parameter	Treatment D (12/3 mg)				Treatment E (16/4 mg)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	30	0.74	0.21	28.65	31	0.78	0.19	24.34
C_{max} (ng/mL)	30	286	155	54.32	31	401	226	56.39
AUC_{last} (hr*pg/mL)	30	647.5	227.4	35.11	31	937.9	368.8	39.33
AUC_{inf} (hr*pg/mL)	30	665.1	230.8	34.70	31	958.4	372.6	38.88
AUC_{Extrap} (%)	30	2.88	1.89	65.63	31	2.32	1.36	58.67
λ_z (hr^{-1})	30	0.1785	0.1626	91.10	31	0.1414	0.1186	83.83
$T_{1/2}$ (hr)	30	6.81	4.45	65.35	31	7.00	3.45	49.21
T_{last} (hr)	30	23.40	8.36	35.71	31	26.97	10.93	40.52
C_{last} (pg/mL)	30	2.06	1.06	51.62	31	2.16	0.952	44.15

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.34, 14.2.35, 14.2.37, 14.2.39, and 14.2.41

Dose proportionality assessments for buprenorphine and naloxone after the dose levels administered in this study included linear regression plots (dose-normalized parameters versus dose fitted with a linear function), power model plots (non-normalized pharmacokinetic parameters versus dose fitted with an exponential power function), and the statistical analyses using a mixed effects model.

Mixed-Effects Model

When all dose levels were included in the dose-proportionality assessment of buprenorphine using a mixed effects model based on a power function, the slope (β1) estimates and associated 90% CIs are summarised in the Table below. The β1 estimates were closer to 1.0000 when the upper dose levels were considered in the power analysis.

Table Assessment of Dose Proportionality using Mixed-Effects Statistical Model Based on a Power Function (Buprenorphine, Norburprenorphine, and Naloxone)

Dependent Variable	Model Variable	Estimate (β_1)	p-value[a]	Lower CI[b]	Upper CI[b]	Dose P[c]
Buprenorphine, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	0.9846	<0.0001	0.9142	1.0550	28.5590
$\ln(AUC_{last})$	ln(Dose)	1.0389	<0.0001	0.9700	1.1078	14.4346
$\ln(C_{max})$	ln(Dose)	0.9327	<0.0001	0.8634	1.0021	8.2158
Norbuprenorphine, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	1.0169	<0.0001	0.9419	1.0918	22.9415
$\ln(AUC_{last})$	ln(Dose)	1.0565	<0.0001	0.9722	1.1408	7.7188
$\ln(C_{max})$	ln(Dose)	1.0301	<0.0001	0.9536	1.1065	14.8814
Naloxone, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	1.1112	<0.0001	1.0451	1.1773	5.0649
$\ln(AUC_{last})$	ln(Dose)	1.1282	<0.0001	1.0605	1.1958	4.3452
$\ln(C_{max})$	ln(Dose)	1.0544	<0.0001	0.9773	1.1314	8.9267

Power Model: $\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon$
where PK is the pharmacokinetic parameter tested,
$\ln(\beta_0)$ is the y-intercept, β_1 is the slope,
and ε is an error term (Subject was used as the random effects term in the analysis)
a = Significant difference from unity (1.0000), defined *a priori* as $p < 0.05$
b = 90% confidence intervals (lower and upper)
c = High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set
Source data: Tables 16.4.3.25, 16.4.3.32, and 16.4.3.39

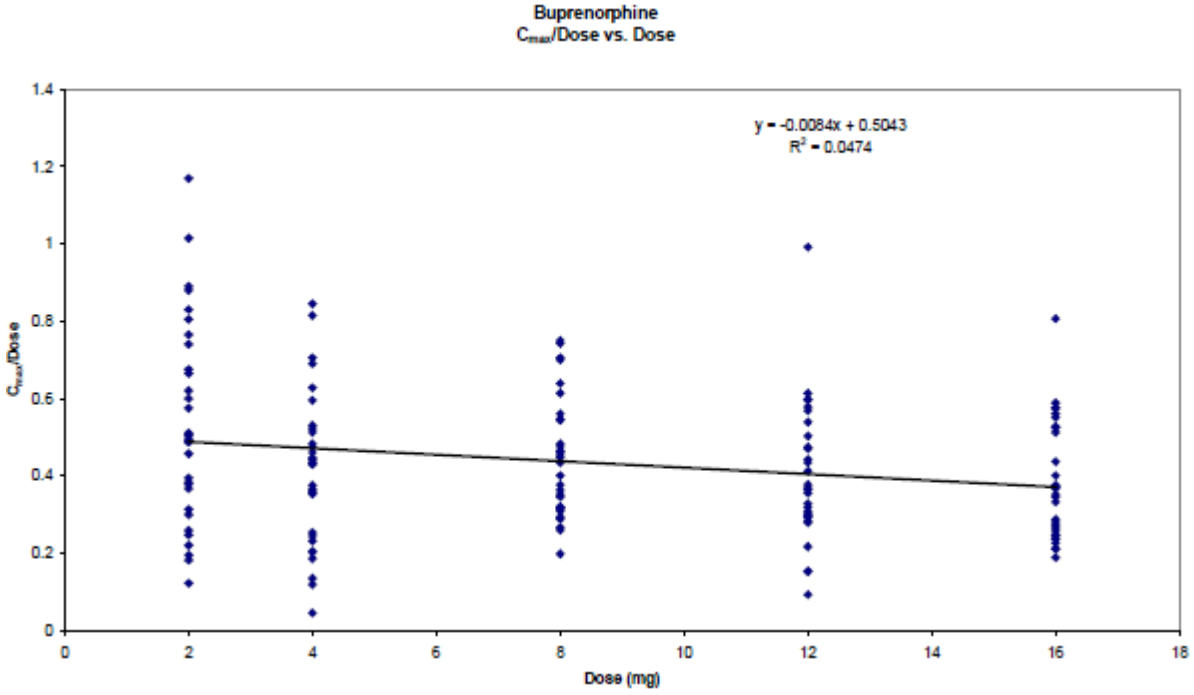
Exposure to buprenorphine, norbuprenorphine, and naloxone increased with increased dose of Suboxone sublingual film. The power analysis results indicated that buprenorphine Cmax and AUCinf and naloxone Cmax were directly proportional to the administered dose of Suboxone sublingual film over the dose range of 2 mg/0.5 mg to 16 mg/4 mg.

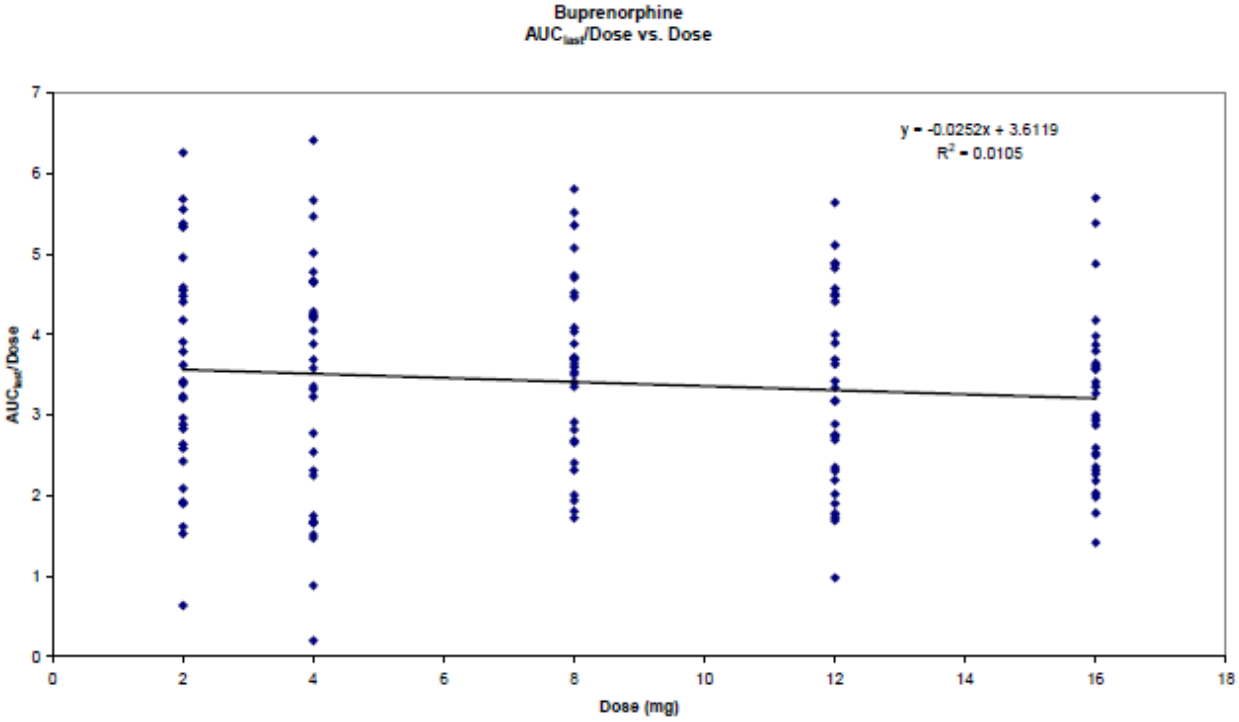
Although the dose proportionality of naloxone AUCinf could not be confirmed over the entire 8-fold dose range, the power analysis indicated that this parameter was proportional over a 5.06-fold range.

Linear regression of dose-normalized values

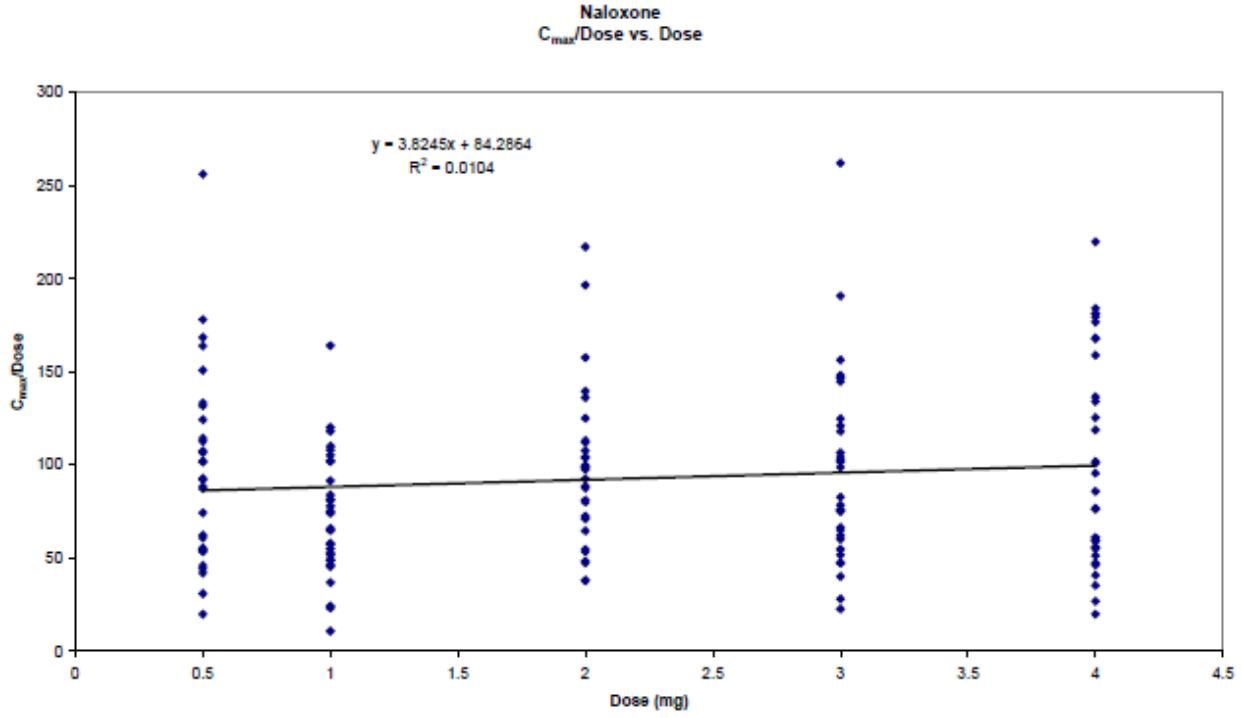
As shown in the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf there was a negative slope (Cmax slope m=-0.0082; AUClast slope m=-0.0252) in the regression line for buprenorphine parameters, suggesting a less than proportional increase in exposure to buprenorphine with increasing dose, and the p-values for slope were small ($p<0.05$).

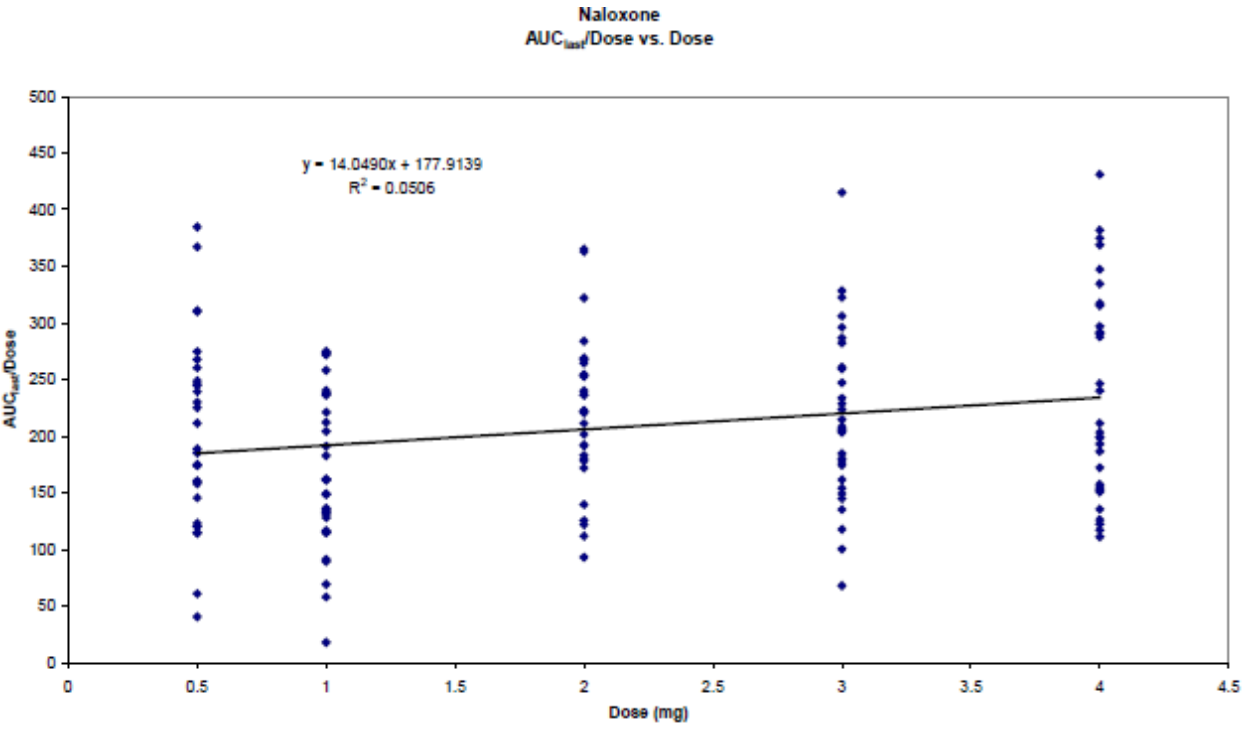
Assessment of Dose-Proportionality in Buprenorphine Exposure (Cmax: upper panel; AUClast: lower panel) after Administration of Test Formulation 1 (Treatment A, 2 mg), Test Formulation 2 (Treatment B, 4 mg), Test Formulation 3 (Treatment C, 8 mg), Test Formulation 4 (Treatment D, 12 mg) and Test Formulation 5 (Treatment E, 16 mg) using Linear Regression and Dose-Normalized Parameter Estimates





Assessment of Dose-Proportionality in Naloxone Exposure (Cmax: upper panel; AUClast: lower panel) after Administration of Test Formulation 1 (Treatment A, 0.5 mg), Test Formulation 2 (Treatment B, 1 mg), Test Formulation 3 (Treatment C, 2 mg), Test Formulation 4 (Treatment D, 3 mg) and Test Formulation 5 (Treatment E, 4 mg) using Linear Regression and Dose-Normalized Parameter Estimates

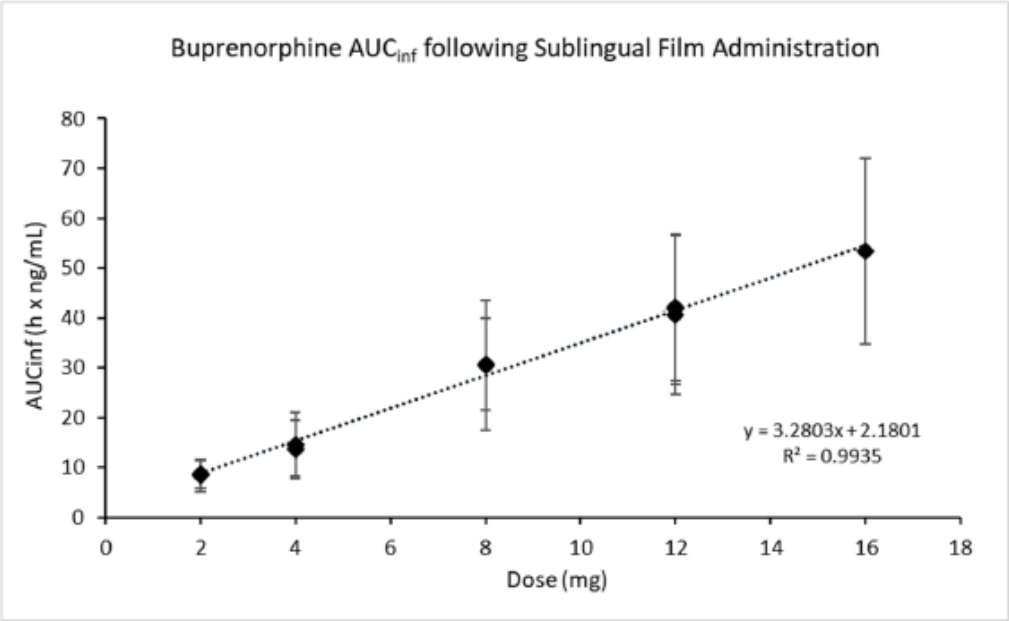




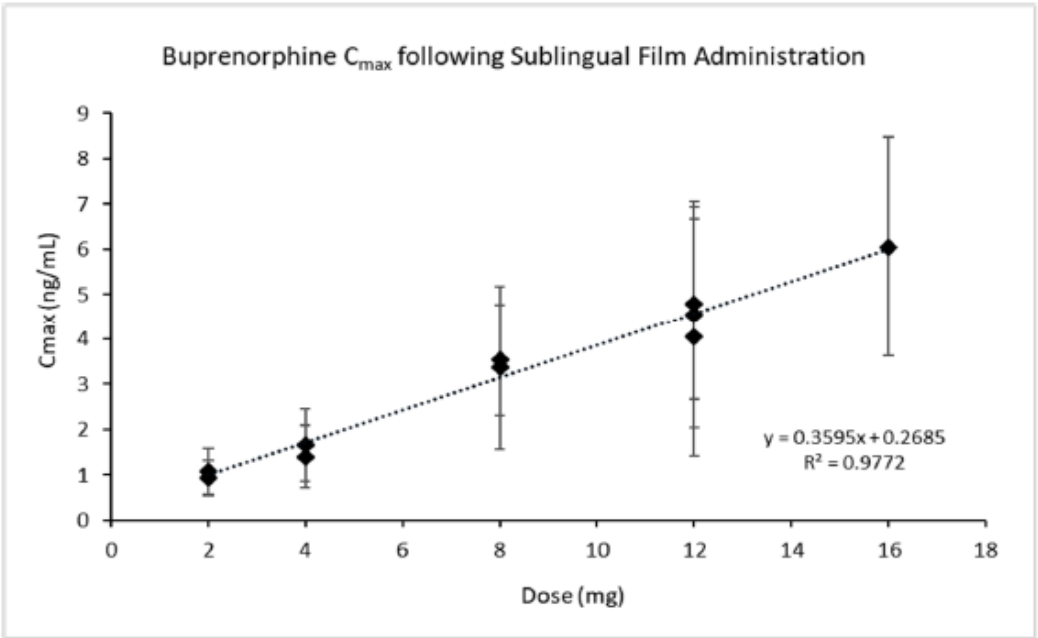
- ***Dose proportionality – Across-study comparison - Sublingual***

Dose-exposure relationships for SL administration of SUBOXONE SL film are summarised in the Figures below using data from the 5 pivotal bioequivalence studies and the dose proportionality study (Study 20-291-SA).

Figure Dose-Exposure Relationship for Buprenorphine Following SL Administration of Buprenorphine / Naloxone Film

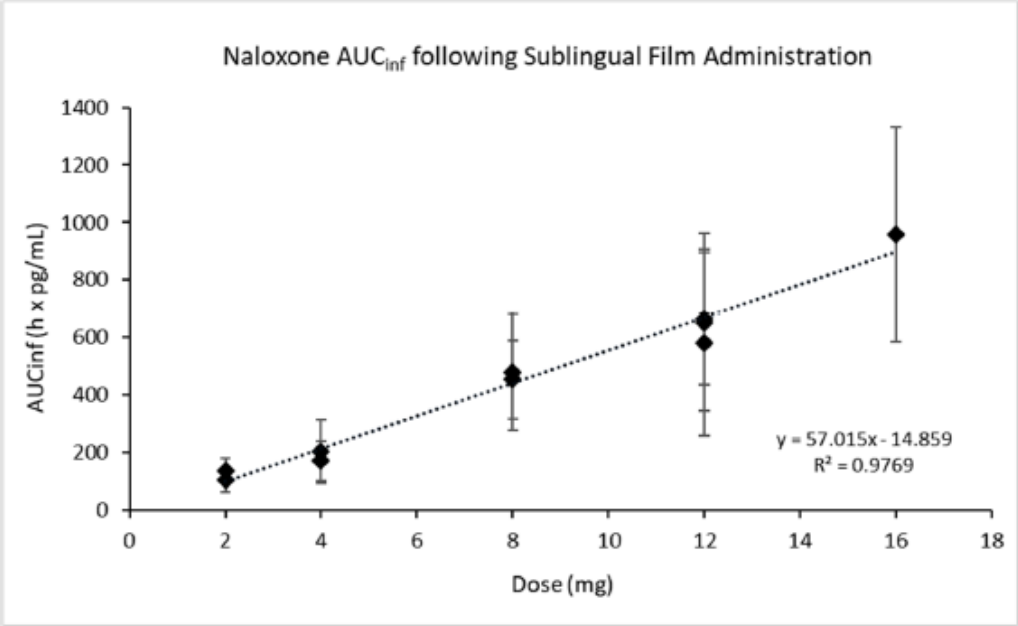


Data derived from Studies 20-250-SA (Table 11.4.3.4), 20-272-SA (Table 11.4.3.4), 20-273-SA (Table 11.4.3.4), 20-B20-AU (Table 11.4.3.4), 1003395 (Table 11.4.3.4), 20-291-SA (Table 11.4.3.4).

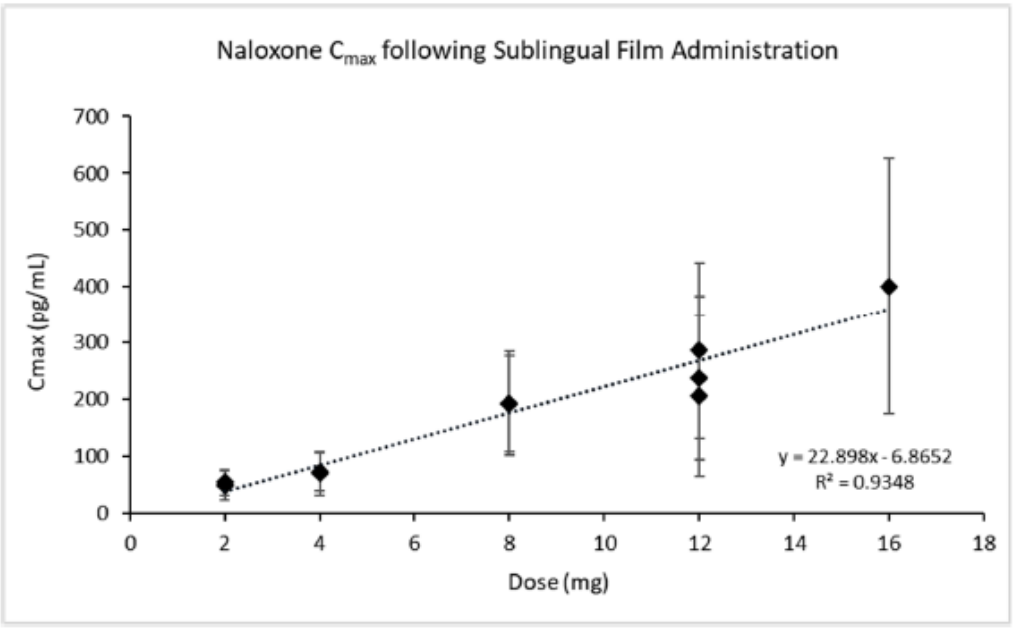


Data derived from Studies 20-250-SA (Table 11.4.3.4), 20-272-SA (Table 11.4.3.4), 20-273-SA (Table 11.4.3.4), 20-B20-AU (Table 11.4.3.4), 1003395 (Table 11.4.3.4), 20-291-SA (Table 11.4.3.4).

Figure Dose-Exposure Relationship for Naloxone Following SL Administration of Buprenorphine/Naloxone Film



Data derived from Studies 20-250-SA (Table 11.4.3.6), 20-272-SA (Table 11.4.3.6), 20-273-SA (Table 11.4.3.6), 20-B20-AU (Table 11.4.3.6), 1003395 (Table 11.4.3.6), 20-291-SA (Table 11.4.3.8).



Data derived from Studies 20-250-SA (Table 11.4.3.6), 20-272-SA (Table 11.4.3.6), 20-273-SA (Table 11.4.3.6), 20-B20-AU (Table 11.4.3.6), 1003395 (Table 11.4.3.6), 20-291-SA (Table 11.4.3.8).

- ***Dose proportionality - Buccal***

Study 20-293-SA

Dose proportionality study to compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buprenorphine/naloxone film strip (buccal) investigational formulations, manufactured by MonoSol Rx, LLC for Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.

Table Pharmacokinetic Parameters of Buprenorphine

Parameter	Treatment A: 2/0.5 mg				Treatment B: 4/1 mg				Treatment C: 8/2 mg			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	33	1.61	0.63	39.14	32	1.68	0.74	43.66	32	1.56	0.56	35.97
C_{max} (ng/mL)	33	0.944	0.405	42.85	32	1.62	0.655	40.44	32	3.55	1.85	52.09
AUC_{last} (hr*ng/mL)	33	7.255	2.634	36.31	32	14.65	5.481	37.42	32	32.30	12.56	38.90
AUC_{inf} (hr*ng/mL)	31	8.409	2.904	34.54	32	16.11	5.744	35.65	32	34.04	13.17	38.70
AUC_{Extrap} (%)	31	12.12	5.33	43.97	32	9.43	4.38	46.44	32	5.26	2.22	42.26
λ_z (hr^{-1})	31	0.0399	0.0153	38.43	32	0.0321	0.0131	40.97	32	0.0230	0.0073	31.75
$T_{1/2}$ (hr)	31	20.34	9.39	46.15	32	26.76	17.18	64.22	32	33.54	12.26	36.56
T_{last} (hr)	33	46.55	13.33	28.65	32	71.25	25.49	35.77	32	111.75	25.58	22.89
C_{last} (ng/mL)	33	0.0346	0.00852	24.65	32	0.0405	0.0200	49.37	32	0.0356	0.0138	38.73

Parameter	Treatment D: 12/3 mg				Treatment E: 16/4 mg			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	36	1.79	0.60	33.62	35	1.53	0.51	33.13
C_{max} (ng/mL)	36	4.54	1.83	40.21	35	5.77	1.96	33.89
AUC_{last} (hr*ng/mL)	36	44.91	16.37	36.44	35	54.91	15.08	27.46
AUC_{inf} (hr*ng/mL)	36	47.15	17.39	36.88	35	57.37	15.99	27.87
AUC_{Extrap} (%)	36	4.67	2.16	46.21	35	4.15	1.83	44.20
λ_z (hr^{-1})	36	0.0216	0.0085	39.42	35	0.0207	0.0078	37.82
$T_{1/2}$ (hr)	36	36.26	11.55	31.86	35	37.98	13.55	35.69
T_{last} (hr)	36	127.33	22.82	17.92	35	132.34	18.75	14.17
C_{last} (ng/mL)	36	0.0405	0.0186	45.80	35	0.0427	0.0162	38.00

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.16 - 14.2.20

Exposure to buprenorphine increased with dose of buprenorphine in the films strips. On average, peak exposure to buprenorphine was observed from 1.5 to 1.8 hr and mean estimates of Cmax ranged from 0.944 ± 0.405 ng/mL after 2/0.5 mg to 5.77 ± 1.96 ng/mL after 16/4 mg. Likewise, overall systemic exposure, based on AUC values, increased with dose. Mean estimates of AUClast ranged from 7.255 ± 2.634 hr*ng/mL after 2/0.5 mg to 54.91 ± 15.08 hr*ng/mL after 16/4 mg.

Table Pharmacokinetic Parameters of Naloxone

Parameter	Treatment A: 2/0.5 mg n	Mean	SD	CV%	Treatment B: 4/1 mg n	Mean	SD	CV%	Treatment C: 8/2 mg n	Mean	SD	CV%
T_{max} (hr)	33	0.80	0.25	30.89	32	0.80	0.19	23.46	32	0.80	0.26	32.31
C_{max} (pg/mL)	33	44.0	13.5	30.80	32	77.6	29.4	37.85	32	196	78.2	39.98
AUC_{last} (hr*pg/mL)	33	109.4	32.71	29.90	32	201.5	64.05	31.79	32	505.3	174.0	34.44
AUC_{inf} (hr*pg/mL)	33	116.4	38.14	32.78	32	209.5	65.54	31.28	32	521.3	176.0	33.75
AUC_{Extrap} (%)	33	5.38	4.62	85.86	32	3.96	2.49	62.84	32	3.36	2.15	64.05
λ_z (hr^{-1})	33	0.3525	0.1599	45.36	32	0.2674	0.1231	46.02	32	0.1612	0.1331	82.55
$T_{1/2}$ (hr)	33	2.85	3.02	106.06	32	3.59	2.52	70.03	32	7.05	4.09	57.96
T_{last} (hr)	33	11.15	4.00	35.88	32	14.69	6.30	42.87	32	23.25	9.11	39.20
C_{last} (pg/mL)	33	1.57	0.543	34.66	32	1.68	0.738	44.06	32	1.96	1.29	65.62

Parameter	Treatment D: 12/3 mg n	Mean	SD	CV%	Treatment E: 16/4 mg n	Mean	SD	CV%
T_{max} (hr)	36	0.77	0.25	32.87	35	0.73	0.21	28.69
C_{max} (pg/mL)	36	289	142	48.97	35	413	181	43.73
AUC_{last} (hr*pg/mL)	36	754.9	238.2	31.55	35	1068	390.6	36.57
AUC_{inf} (hr*pg/mL)	36	775.4	238.2	30.72	35	1089	390.3	35.84
AUC_{Extrap} (%)	36	2.84	2.96	104.03	35	2.15	1.68	78.45
λ_z (hr^{-1})	36	0.1099	0.0886	80.60	35	0.1060	0.0599	56.55
$T_{1/2}$ (hr)	36	8.03	3.21	39.92	35	8.16	3.75	45.97
T_{last} (hr)	36	30.00	9.30	30.98	35	32.92	9.80	29.78
C_{last} (pg/mL)	36	1.71	0.852	49.86	35	1.81	0.802	44.34

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.26 - 14.2.30

Mixed Effects Model

The results of the power analyses using a linear effects model are summarized in the Table below.

Table Assessment of Dose Proportionality using Mixed-Effects Statistical Model Based on a Power Function

Dependent Variable	Model Variable	Estimate (β_1)	p-value[a]	Lower CI[b]	Upper CI[b]	Dose P[c]
Buprenorphine, Dose Range 2/0.5 mg to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	0.9507	<0.0001	0.9180	0.9835	33.3474
$\ln(AUC_{last})$	ln(Dose)	0.9979	<0.0001	0.9645	1.0314	3295.4151
$\ln(C_{max})$	ln(Dose)	0.8904	<0.0001	0.8488	0.9319	6.7053
Buprenorphine, Dose Range 4/1 mg to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	0.9496	<0.0001	0.8940	1.0051	15.0990
$\ln(AUC_{last})$	ln(Dose)	0.9919	<0.0001	0.9361	1.0476	90.2061
$\ln(C_{max})$	ln(Dose)	0.9589	<0.0001	0.8833	1.0346	11.7600
Buprenorphine, Dose Range 2/0.5 mg to 16/4 mg Excluding Subjects 507, 511, 534, and 543						
$\ln(AUC_{inf})$	ln(Dose)	0.9458	<0.0001	0.9132	0.9784	27.4771
$\ln(AUC_{last})$	ln(Dose)	0.9898	<0.0001	0.9573	1.0223	847.2955
$\ln(C_{max})$	ln(Dose)	0.8885	<0.0001	0.8451	0.9319	6.4029

Naloxone, Dose Range 2/0.5 mg to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	1.0715	<0.0001	1.0282	1.1148	12.2483
$\ln(AUC_{last})$	ln(Dose)	1.0897	<0.0001	1.0450	1.1344	8.5098
$\ln(C_{max})$	ln(Dose)	1.0558	<0.0001	0.9966	1.1151	12.1698
Naloxone, Dose Range 2/0.5 mg to 16/4 mg Excluding Subjects 507, 511, 534, and 543						
$\ln(AUC_{inf})$	ln(Dose)	1.0674	<0.0001	1.0235	1.1112	13.2837
$\ln(AUC_{last})$	ln(Dose)	1.0859	<0.0001	1.0406	1.1313	8.9490
$\ln(C_{max})$	ln(Dose)	1.0632	<0.0001	1.0024	1.1240	10.1707

Power Model: $\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon$
where PK is the pharmacokinetic parameter tested,
$\ln(\beta_0)$ is the y intercept, β_1 is the slope,
and ε is an error term (Subject was used as the random effects term in the analysis)
a = Significant difference from unity (1.0000), defined *a priori* as $p < 0.05$
b = 90% confidence intervals (lower and upper)
c = High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

The power analysis curves supported the less than proportional increase in exposure to buprenorphine with increasing dose. When all dose levels were included in the dose-proportionality assessment of buprenorphine using a mixed effects model based on a power function, the β1 estimates for buprenorphine and associated 90% confidence intervals were 0.8904 (0.8488, 0.9319) for Cmax, 0.9979 (0.9645, 1.0314) for AUClast, and 0.9507 (0.9180, 0.9835) for AUCinf.

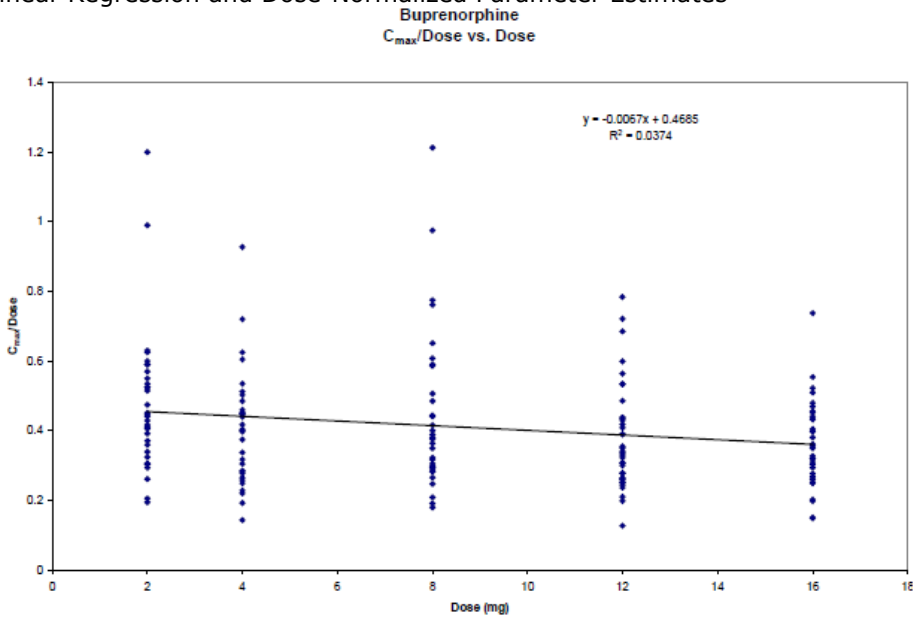
Hence, dose proportionality for buprenorphine AUCinf and Cmax could not be confirmed over the entire 8-fold dose range, the power analysis indicated that the Cmax parameter was proportional over a 6.7-fold range.

The confidence interval for AUClast, however, included 1.000 and dose proportionality may be concluded over the 2/0.5 mg to 16/4 mg range.

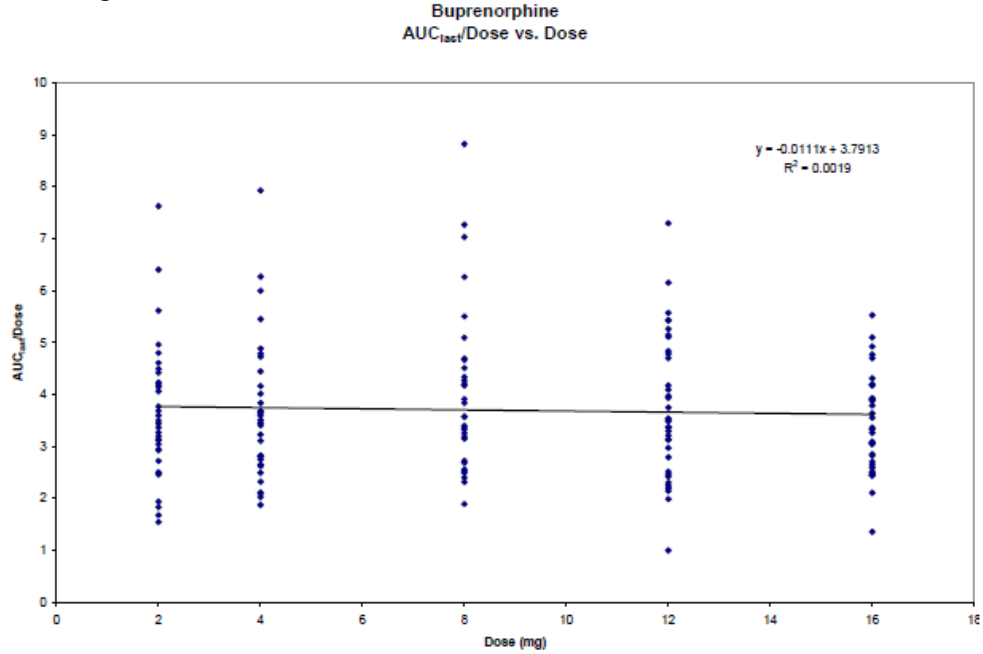
Linear regression of dose-normalized values

As shown in the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf, there was a negative slope in the regression line for buprenorphine Cmax parameters, suggesting a less than proportional increase in exposure to buprenorphine with increasing dose, and the p-values for slope were small ($p<0.05$).

Assessment of Dose-Proportionality in Peak Buprenorphine Exposure (Cmax) after Administration of Test Formulation 1 (Treatment A, 2 mg), Test Formulation 2 (Treatment B, 4 mg), Test Formulation 3 (Treatment C, 8 mg), Test Formulation 4 (Treatment D, 12 mg) and Test Formulation 5 (Treatment E, 16 mg) using Linear Regression and Dose-Normalized Parameter Estimates

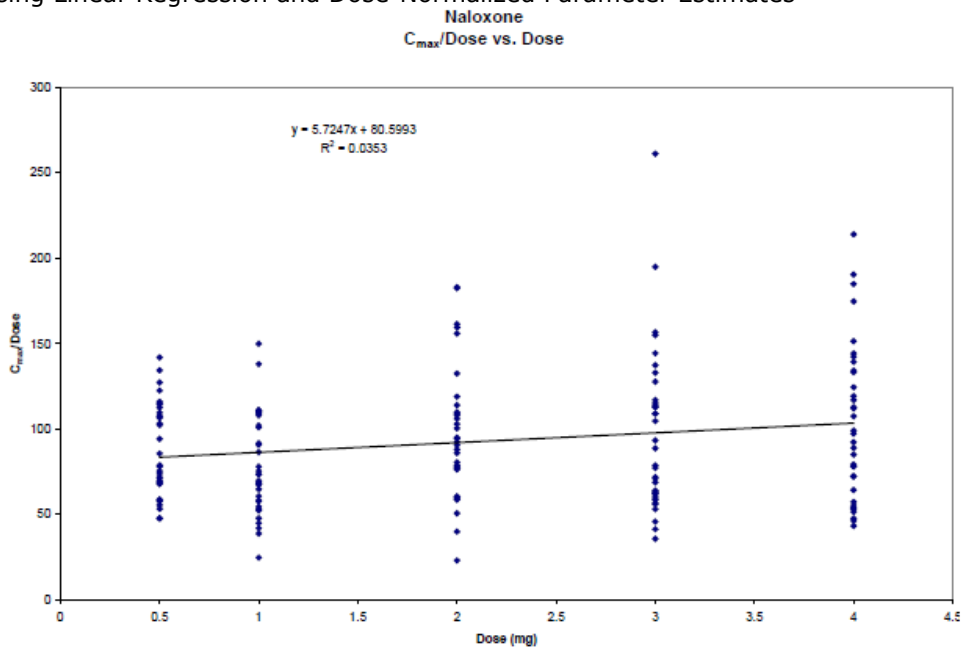


Assessment of Dose-Proportionality in Overall Buprenorphine Exposure (AUClast) after Administration of Test Formulation 1 (Treatment A, 2 mg), Test Formulation 2 (Treatment B, 4 mg), Test Formulation 3 (Treatment C, 8 mg), Test Formulation 4 (Treatment D, 12 mg) and Test Formulation 5 (Treatment E, 16 mg) using Linear Regression and Dose-Normalized Parameter Estimates



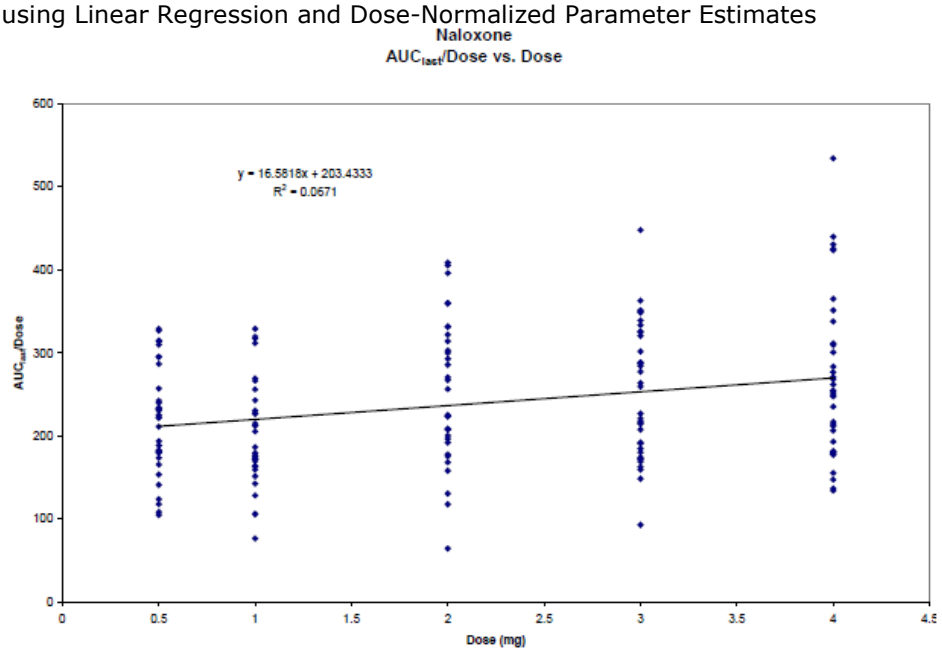
Unlike buprenorphine, there was a slightly positive slope in the regression line for dose-normalized values of Cmax, AUClast, and AUCinf for naloxone, suggesting a greater than proportional increase in exposure to naloxone with increasing dose, and the p-values for slope were small ($p<0.05$). Although a positive slope was observed in the linear trend line, in general, the dose-normalized parameter values were within the same range across doses.

Assessment of Dose-Proportionality in Peak Naloxone Exposure (Cmax) after Administration of Test Formulation 1 (Treatment A, 0.5 mg), Test Formulation 2 (Treatment B, 1 mg), Test Formulation 3 (Treatment C, 2 mg), Test Formulation 4 (Treatment D, 3 mg) and Test Formulation 5 (Treatment E, 4 mg) using Linear Regression and Dose-Normalized Parameter Estimates



Assessment of Dose-Proportionality in Overall Naloxone Exposure (AUClast) after Administration of Test Formulation 1 (Treatment A, 0.5 mg), Test Formulation 2 (Treatment B, 1 mg), Test Formulation 3 (Treatment C, 2 mg), Test Formulation 4 (Treatment D, 3 mg) and Test Formulation 5 (Treatment E, 4 mg)

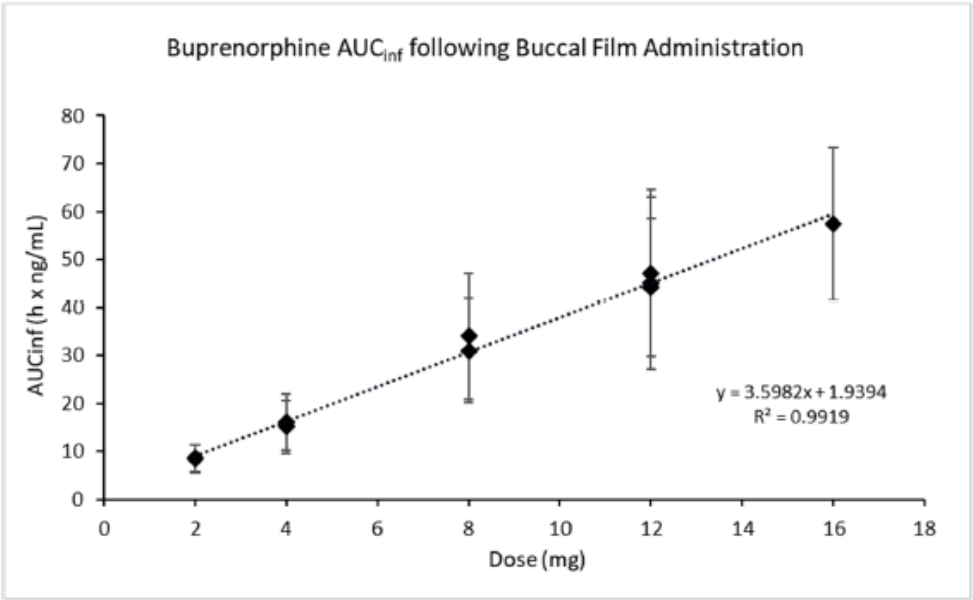
using Linear Regression and Dose-Normalized Parameter Estimates



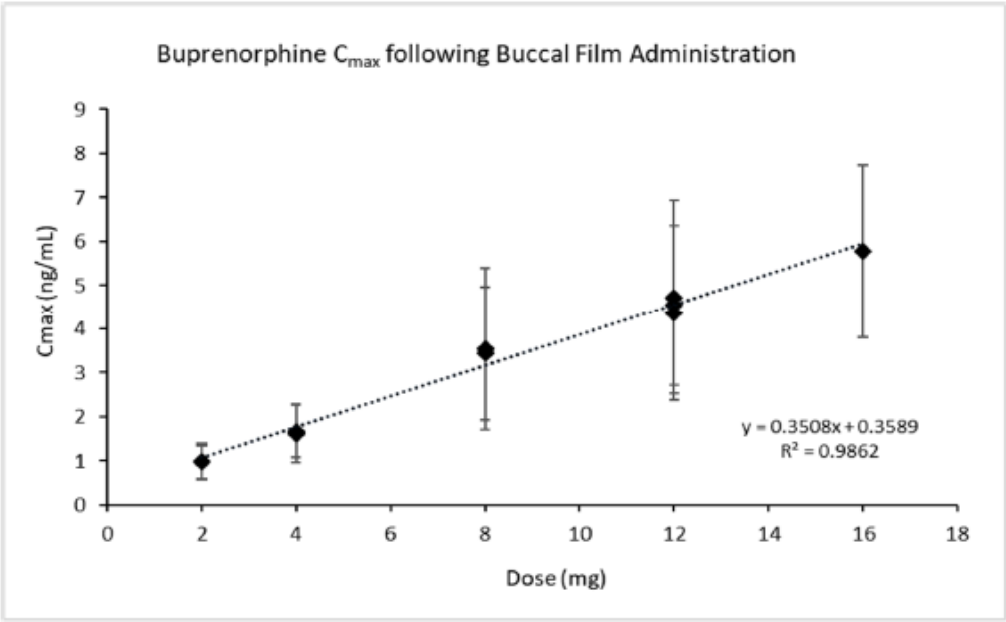
- ***Dose proportionality – Across-study comparison - Buccal***

Dose-exposure relationships for buccal administration of Suboxone SL film are summarised in the Figures below using data from the 5 pivotal bioequivalence studies and the dose proportionality study (Study 20-293-SA).

Dose-Exposure Relationship for Buprenorphine Following Buccal Administration of Buprenorphine/Naloxone Film

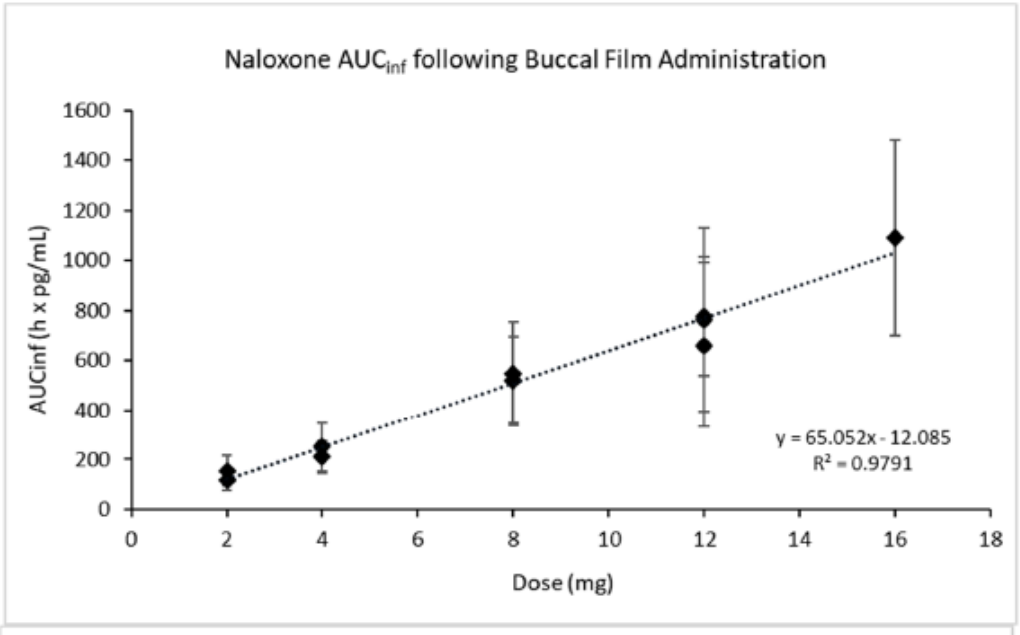


Data derived from Studies 20-250-SA (Table 11.4.3.4), 20-272-SA (Table 11.4.3.4), 20-273-SA (Table 11.4.3.4), 20-B20-AU (Table 11.4.3.4), 1003395 (Table 11.4.3.4), 20-293-SA (Table 11.4.3.4).

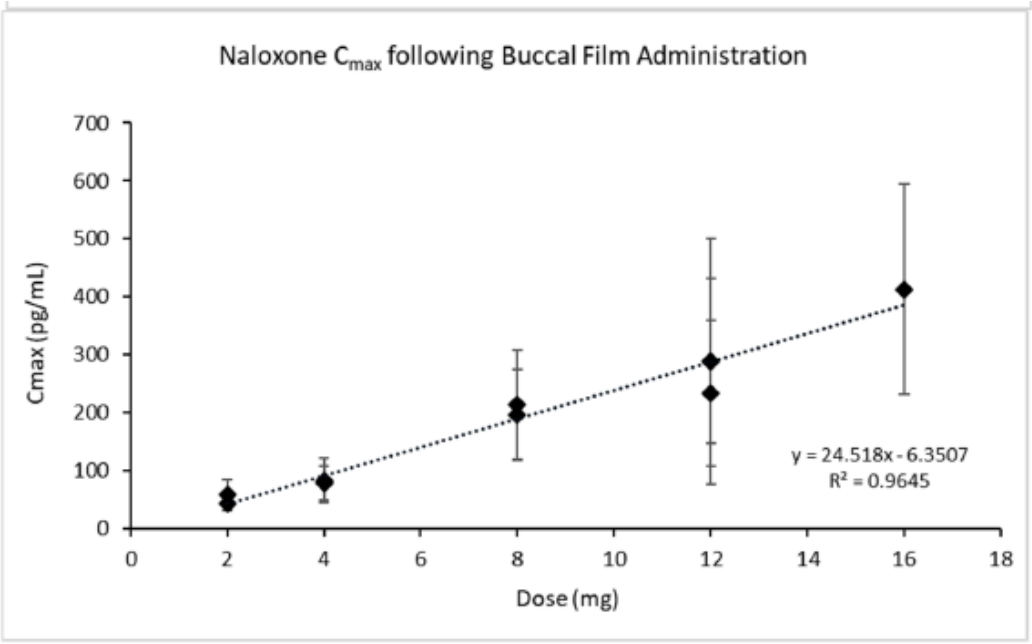


Data derived from Studies 20-250-SA (Table 11.4.3.4), 20-272-SA (Table 11.4.3.4), 20-273-SA (Table 11.4.3.4), 20-B20-AU (Table 11.4.3.4), 1003395 (Table 11.4.3.4), 20-293-SA (Table 11.4.3.4).

Dose-Exposure Relationship for Naloxone Following Buccal Administration of Buprenorphine/Naloxone Film



Data derived from Studies 20-250-SA (Table 11.4.3.6), 20-272-SA (Table 11.4.3.6), 20-273-SA (Table 11.4.3.6), 20-B20-AU (Table 11.4.3.6), 1003395 (Table 11.4.3.6), 20-293-SA (Table 11.4.3.8).



Data derived from Studies 20-250-SA (Table 11.4.3.6), 20-272-SA (Table 11.4.3.6), 20-273-SA (Table 11.4.3.6), 20-B20-AU (Table 11.4.3.6), 1003395 (Table 11.4.3.6), 20-293-SA (Table 11.4.3.8).

In-vivo Disintegration Time

Summary of In-Vivo Disintegration Profiles Following Sublingual or Buccal Administration of Buprenorphine / Naloxone Film Versus Sublingual Administration of Buprenorphine/Naloxone Tablet

For the 5 pivotal bioequivalence studies and the 2 dose proportionality studies, disintegration times for Suboxone SL film administered sublingually and buccally were assessed and compared to Suboxone SL tablets.

Following administration of the test or reference formulation, the research staff inspected the subject's mouth cavity to determine when the formulation had disintegrated. The inspection occurred either 15 minutes following drug administration or when a subject indicated that the film had completely disintegrated, whichever occurred first. Using a prearranged hand signal, the subjects indicated when, in their judgment, complete disintegration of the film had occurred. A member of the research staff recorded the time of the subject's hand signal. A mouth check was performed using a flashlight and a tongue depressor, immediately after a subject indicated that the drug completely disintegrated. If the drug had not disintegrated completely, the subject was instructed to continue holding the drug in place until complete disintegration occurred. A member of the research staff then recorded the time of complete disintegration. After a subject indicated complete disintegration of the film and the research staff member provided confirmation, the subject was informed that he or she could swallow.

2.4.3. Pharmacodynamics

There were no pharmacodynamic studies conducted as part of this MAA for the new film strip formulation and none are required.

2.4.4. Discussion on clinical pharmacology

PK Similarity between the SL tablet and film formulation

Across the five SD bioequivalence studies the newly developed film formulation (administered sublingually and buccally) was compared with the established Suboxone SL tablets over the 2/0.5 mg to 12/3 mg dose range. A variety of results (both complying and exceeding the 80-125% acceptance range for BE) was obtained for Cmax resp. AUC of the two buprenorphine and naloxone analytes. While for the lower dose strengths (2/0.5 mg to 8/2 mg) exposure in buprenorphine / naloxone was more similar between the film and tablet dosage form, the difference between the two formulations was most apparent for the highest 12/3 mg dose strength yielding point estimators of 143.49 [127.99 – 160.86 CIs] for sublingual and 151.73 [137.84 – 167.02 CIs] for buccal buprenorphine Cmax.

In the present line extension procedure, consistent compliance with the formal BE acceptance criteria (90% CIs within 80-125%) is not considered an indispensable prerequisite for approvability. The issue is adequately addressed in section 4.2 of the proposed SmPC. Accordingly, when switching patients from the established tablets to the newly developed film formulation, the subject should start using the same nominal dose. Thereafter, dose adjustment may be necessary:

Switching between sublingual tablet and film (where applicable)

Patients being switched between Suboxone sublingual tablets and Suboxone film should be started on the same dose as the previously administered medicinal product. However, dose adjustments may be necessary when switching between medicinal products. Due to the potentially greater relative bioavailability of

Suboxone film compared to Suboxone sublingual tablets, patients switching from sublingual tablets to film should be monitored for over-dose. Those switching from film to sublingual tablets should be monitored for withdrawal or other indications of under-dosing. In clinical studies, the pharmacokinetics of Suboxone film were not consistently shown to be similar to the respective dosage strengths of Suboxone sublingual tablets, as well as to the combinations (see section 5.2). If switching between Suboxone film and Suboxone sublingual tablets, the patient should be monitored in case a need to readjust the dose occurs. Combining different formulations or alternating between film and sublingual tablet formulations is not advised.

Overall, BE could not consistently be shown across all dose strengths. The proposed SmPC wording takes due account of similar, however, not consistently bioequivalent blood levels between the SL tablet and SL / buccal film formulation. When the patient is switched from tablets to films, the patient should be monitored for over-medication. In the reverse case, switching from films to tablets, the patients should be monitored for withdrawal or other signs of under-medication.

Switch between SL and buccal film administration

As concerns the potential switch between the two modes of administration of the film formulation, however, the SmPC specifies that no further monitoring is required based on similarity of exposure:

Switching between sublingual and buccal sites of administration

The systemic exposure of buprenorphine between buccal and sublingual administration of Suboxone film is approximately similar (see section 5.2). Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

The comparison between the SL and buccal administration of the film formulation does not yield consistently bioequivalent exposure of buprenorphine / naloxone across the five pivotal SD BE studies. However, in the three BE studies focussing on single unit administration of the film (20-250-SA: 1 x 2/0.5 mg, 20-273-SA: 1 x 8/2 mg, 20-B20-AU: 1 x 12/3 mg) bioequivalent exposure of buprenorphine could be demonstrated between the two methods of administration. The proposed SmPC wording pointing to approximately similar systemic buprenorphine exposure allowing the switch between the sublingual and buccal film administration is therefore considered acceptable.

Completeness of the data package

The newly developed 4/1 mg film formulation strength was neither included in any of the five SD BE studies nor in one of the two dose proportionality studies. Provision of in vivo data on the 4/1 mg dose strength can be waived since the 2/0.5 mg and 4/1 mg film dose strengths are obtained from the same bulk, hence are dose weight multiples (2/0.5 mg: 22 x 12.8 mm [40 mg nominal weight], 4/1 mg: 22 x 25.6 mm [80 mg nominal weight]). Therefore, the BE study results obtained with the 2/0.5 mg formation can be extrapolated to the dose proportional 4/1 mg dose strength. Bioequivalence between the 2/0.5 mg film and SL tablet formulation was tested in study 20-250-SA (1 x 2/0.5 mg) and 20-272-SA (2 x 2/0.5 mg). Given the linear increase of Cmax and AUC with increasing doses (2/05 mg to 16/4 mg dose range) both across studies and within dose proportionality studies (sublingual administration: 20-291-SA, buccal administration: 20-293-SA) it is therefore justified to waive generating in vivo PK data for the 4/1 mg dose strength.

Dose linearity after sublingual administration – Study 20-291-SA

In the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf, there was a negative slope in the regression line, suggesting a less than proportional increase in exposure to

buprenorphine with increasing dose. For naloxone, small positive slopes were calculated for AUC and Cmax suggesting a slightly more than dose proportional increase in naloxone exposure with increasing doses.

When all dose levels were included in the dose-proportionality assessment of buprenorphine using a mixed effects model based on a power function, the β1 estimates for slope and associated 90% confidence intervals were 0.9327 (0.8634, 1.0021) for Cmax, 1.0389 (0.9700, 1.1078) for AUClast, and 0.9846 (0.9142, 1.0550) for AUCinf. The power analysis results indicated that buprenorphine exposure was directly proportional to the administered dose of buprenorphine/naloxone film strips over the dose range considered in this study, 2/0.5 mg to 16/4 mg.

In conclusion, it was shown that the new film strip formulation displays linear, however, not fully dose proportional increases in plasma concentrations in doses between 2/0.5 and 16/4 mg buprenorphine/naloxone after sublingual administration. Study 20-291-SA is limited by the fact that the dose range examined (2/0.5 mg to 16/4 mg) does not cover the maximum daily dose (24/6 mg according to the SmPC) and that the 4/1 mg dose was administered as 2 x 2/0.5 mg film instead of the newly developed 4/1 mg film formulation.

Dose linearity after buccal administration – Study 20-293-SA

Linearity could be demonstrated for the 4/1 mg to 16/4 mg dose range, however, not covering the entire range of newly developed film formulations (2/0.5 mg to 16/4 mg). This information is adequately reflected in SmPC section 5.2:

Linearity / non-linearity
Buprenorphine Cmax and AUC increased in a linear fashion with the increasing dose (in the range 4-16 mg), although the increase was not directly dose-proportional.

The less than proportional increase in exposure of buprenorphine with increasing dose was visualised in the linear regression plots of Cmax, AUClast, and AUCinf (negative slope for buprenorphine Cmax and AUC). On the other side, increases in naloxone exposure were slightly higher than proportional (indicated by positive slopes in linear regression plots). The reasons for linear, however, slightly less than dose proportional increases in buprenorphine exposure are unknown.

The power analysis using a mixed effects model based on a power function supported the less than proportional increase in exposure to buprenorphine with increasing dose. When all dose levels were included in the dose-proportionality assessment of buprenorphine, the β1 estimates for buprenorphine and associated 90% confidence intervals were <1 [0.8904 (0.8488, 0.9319) for Cmax, 0.9979 (0.9645, 1.0314) for AUClast, and 0.9507 (0.9180, 0.9835) for AUCinf].

Dose linearity after sublingual and buccal administration – Across Study Comparison

Summarized data across studies show that plasma exposures to buprenorphine and naloxone increased linearly with the dose following SL and buccal administration of Suboxone films in the range of 2 mg/0.5 mg to 16 mg/4 mg. Data also show good reproducibility of the results across studies in terms of Cmax and AUC for both naloxone and buprenorphine.

In-vivo disintegration time

Suboxone is administered under supervision of personnel of the opioid dependence treatment unit - at least at treatment initiation. Even in these supervised dosing environments it has been reported that subjects may remove the sublingually placed tablet for subsequent illicit use. Any notable difference in disintegration time between the SL tablets and the films would be considered as a relevant advancement.

The difference in disintegration time was recorded during the five PK studies. It appears that the SL film strips on average disintegrated about 1-5 minutes earlier as compared to the SL tablets. The test product disintegrated about 5 min 30 to 8 min 15 after sublingual placement. There was no clear tendency for extended disintegration times after administration of increasing doses of the SL test. This may be explained by the fact that the size (dimensions) of the film strip does not linearly increase with increasing dose: 2/0.5 mg (22 x 12.8 mm), 4/1 mg (22 x 25.6 mm), 8/2 mg (22 x 12.8 mm), 12/3 mm (22 x 19.2 mm).

The number of film strip units that are administered at once may also be assumed as another potential influential factor on disintegration time. This, is reflected by the comparison of disintegration times recorded in study 20-B20-AU (film administered as 1 x 12/3 mg) with those of study 1003395 (film administered as 1 x 8/2 plus 2 x 2/0.5 mg). In both cases the equal dose was administered. In study 20-B20-AU the single film unit disintegrated within a mean time of 8:15 min, while in study 1003395 (administration of 3 film units) disintegration was complete after a mean of 5:39 min. It therefore appears that disintegration is faster the larger the surface of the administered film strips is.

Interpretation of disintegration data should be made with caution. There appears to be some across study variability in disintegration recording, e.g. mean disintegration of 1 x 8/2 mg plus 2 x 2/0.5 mg SL tablets was recorded in study 1003395 after 8:59 min, while in study 20-B20-AU it took about two minutes longer (10:45 min, the same 3 SL tablet units).

Across all five BE studies mean disintegration of the film formulation took longer after buccal as compared to sublingual administration (20-250-SA: +1:51, 20-272-SA: +1:05, 20-273-SA: +1:36, 20-B20-AU: +3:30, 1003395: + 0:12 min). Comparing the two dose proportionality studies (SL: 20-291-SA, buccal: 20-293-SA), however, disintegration was about 1-2 min faster across all five dose arms after buccal administration.

An even more complex picture is obtained if disintegration between buccal film and SL tablet is compared. Disintegration of the buccal films was faster in three BE studies (20-272-SA: -1:02, 20-273-SA: -4:11, 1003395: -3:08 min), however, for the remaining two BE studies disintegration of the buccal films took longer (20-250-SA: +0:50, 20-B20-AU: +1:00 min).

Removability of administered films

Apart from dissolution time, Lintzeris and co-workers also tested the patients' ability of removing the films 30 sec resp. 1 minute post-administration in relation to the number of film units that were administered sublingually at a time (simultaneous placement of 1-4 films). The authors found that the ability to wholly or partially remove the film was related to the number of films dosed, with more participants able to remove the film when more than two films were dosed at the same time. One minute post-administration no participant (n=36) was able to remove parts of the film if only one film unit was administered. Focussing on removability of the entire film as a whole, no participant was able to remove the entire film within 1 minute if up to two films were administered.

According to more recent literature reports by Larance et al.(2014, 2016), the portion of removal of doses after supervised dosing was found to be about equal between the BNX tablets and BNX films based on surveys conducted in Australian patients being treated within the scope of opioid substitution therapy.

There are strategies to counteract removability of applied doses like e.g. safeguarding that patients moisten their mouth prior to dosing and not applying more than two films at once. Both measures are reflected in the product particulars (please refer to SmPC).

As regards the setting where Suboxone films are administered including the scope of dosing supervision, there may be large differences across the different National Healthcare Systems and underlying legal

frameworks in European Member States. In this regard, there are no differences between the SmPC approved for the Suboxone SL tablets and the one proposed for the newly developed films. At the top of section 4.2 there is an introductory statement saying that treatment must be under the supervision of a physician experienced in the management of opioid dependence / addiction. Furthermore, identical warnings are provided in section 4.4 to alert against misuse, abuse and diversion. This is considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Bioequivalence between film and SL tablets

Across the five pivotal SD bioequivalence studies the newly developed film formulation (administered sublingually and buccally) was compared with the established Suboxone SL tablets over the 2/0.5 mg to 12/3 mg dose range. A variety of results (both complying and exceeding the 80-125% acceptance range for BE) was obtained for Cmax resp. AUC of the two buprenorphine and naloxone analytes.

In the present line extension procedure, consistent compliance with the formal BE acceptance criteria (90% CIs within 80-125%) is not considered an indispensable prerequisite for approvability. The issue is adequately addressed in the amended SmPC section 4.2. Accordingly, when switching patients from the established tablets to the newly developed film formulation, the subject should start using the same nominal dose. Thereafter, dose adjustment may be necessary. When the patient is switched from tablets to films, the patient should be monitored for over-medication. In the reverse case, switching from films to tablets, the patients should be monitored for withdrawal or other signs of under-medication.

Overall, BE could not consistently be shown across all dose strengths. The SmPC wording takes due account of approximately similar, however, not consistently bioequivalent blood levels between the SL tablet and SL / buccal film formulation.

Switch between sublingual and buccal film

As concerns the potential switch between the two modes of administration of the film formulation, however, the SmPC specifies that no further monitoring is required based on approximate similarity of exposure.

The comparison between the SL and buccal administration of the film formulation does not yield consistently bioequivalent exposure of buprenorphine / naloxone across the five pivotal SD BE studies. At least, in the three BE studies focussing on single unit administration of the film (20-250-SA: 1 x 2/0.5 mg, 20-273-SA: 1 x 8/2 mg, 20-B20-AU: 1 x 12/3 mg) bioequivalent exposure of buprenorphine could be demonstrated between the two methods of administration. The SmPC wording pointing to approximately similar systemic buprenorphine exposure (incl. reference to section 5.2) allowing the switch between the sublingual and buccal film administration is therefore considered acceptable.

Biowaiver for the 4/1 mg film dose strength

The newly developed 4/1 mg film formulation strength was neither included in any of the five SD BE studies nor in one of the two dose proportionality studies. Therefore, the BE study results obtained with the 2/0.5 mg formation can be extrapolated to the dose proportional 4/1 mg dose strength. Given the linear increase of Cmax and AUC with increasing doses (2/05 mg to 16/4 mg dose range), both across studies and within dose proportionality studies, it is therefore justified to waive generating in vivo PK data for the 4/1 mg dose strength.

Dose proportionality

Two dose proportionality studies were conducted, one for each method of administration (20-291-SA for sublingual, resp. 20-293-SA for buccal administration). Five dose arms were included (2/0.5 mg, 2 x 2/0.5 mg, 1 x 8/2 mg, 1 x 12/3 mg, 1 x 16/4 mg). The 16/4 mg film formulation is not subject of the present MAA.

In the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf (both for sublingual and buccal), there was a negative slope in the regression line, suggesting a less than proportional increase in exposure to buprenorphine with increasing dose. For naloxone, small positive slopes were calculated for AUC and Cmax suggesting a slightly more than dose proportional increase in naloxone exposure with increasing doses.

When all dose levels were included in the dose-proportionality assessment (sublingual) of buprenorphine using a mixed effects model based on a power function, the power analysis results indicated that buprenorphine exposure was directly proportional to the administered dose of buprenorphine/naloxone film strips over the dose range considered in this study, 2/0.5 mg to 16/4 mg.

Based on the mixed effects model for buccal administration, linearity could only be demonstrated for the 4/1 mg to 16/4 mg dose range, therefore, not covering the entire range of newly developed film formulations (2/0.5 mg to 16/4 mg). This information is adequately reflected in SmPC section 5.2.

Both dose proportionality studies are limited by the fact that the dose range examined (2/0.5 mg to 16/4 mg) does not cover the maximum daily dose (24/6 mg according to the SmPC) and that the 4/1 mg dose was administered as 2 x 2/0.5 mg film instead of the newly developed 4/1 mg film formulation.

Including data of across study comparisons, in summary, it was shown that plasma exposures to buprenorphine and naloxone increased linearly with the dose across studies following either SL or buccal administration of Suboxone SL film in the range of 2 mg/0.5 mg to 16 mg/4 mg. Data also show reasonable reproducibility of the results across studies in terms of Cmax and AUC for both naloxone and buprenorphine.

In vivo disintegration time

Suboxone is administered under supervision of personnel of the opioid dependence treatment unit - at least at treatment initiation. Even in these supervised dosing environments it has been reported that subjects may remove the sublingually placed tablet for subsequent illicit use. Any notable difference in disintegration time between the SL tablets and the films would be considered as a relevant advancement.

The benefit of the new film formulation in terms of acceleration of sublingual disintegration time (as compared to the SL tablets) appears small. During the BE studies, the SL film strips disintegrated on average about 1-3 minutes earlier as compared to the SL tablets (after about 5-8 min vs 7-11 min).

The small difference in disintegration time between the film and tablet formulation was confirmed in the literature study referenced by the Applicant. A group of Australian authors (Lintzeris et al 2013) compared buprenorphine/naloxone SL tablets and SL films and found a difference in dissolution time of only 1 minute (173 $\pm$ 71 vs 242 $\pm$ 141 seconds) in n=92 OUD patients.

Removability of administered films

In line with the small differences in disintegration time between tablets and films, removability of administered doses (even after supervised dosing) is likely to remain an issue in opioid substitution therapy with Suboxone.

The patients' ability of removing the films 30 sec resp. 1 minute post-administration in relation to the number of film units that were administered sublingually at a time (simultaneous placement of 1-4 films) was tested by Lintzeris and co-workers (literature provided by the Applicant). The authors found that the ability to

wholly or partially remove the film was related to the number of films dosed, with more participants able to remove the film when more than two films were dosed at the same time. One minute post-administration no participant (n=36) was able to remove parts of the film if only one film unit was administered. Focussing on removability of the entire film as a whole, no participant was able to remove the entire film within 1 minute if up to two films were administered.

More recent literature reports by Larance et al.(2014, 2016) demonstrated that the portion of removal of doses after supervised dosing was about equal between the BNX tablets and BNX films based on surveys conducted in Australian patients being treated within the scope of opioid substitution therapy (N=543).

There are strategies to counteract removability of applied doses like e.g. safeguarding that patients moisten their mouth prior to dosing and not applying more than two films at once.

As regards the setting where Suboxone films are administered including the scope of dosing supervision, there may be large differences across the different National Healthcare Systems and underlying legal frameworks in European Member States. In this regard, there are no differences between the SmPC approved for the Suboxone SL tablets and the one proposed for the newly developed films. At the top of section 4.2 there is an introductory statement saying that treatment must be under the supervision of a physician experienced in the management of opioid dependence / addiction. Furthermore, identical warnings are provided in section 4.4 to alert against misuse, abuse and diversion. This is considered acceptable.

In summary, the PK profile of the newly developed film formulation was reasonably characterized. The overall essence of the five BE studies was that buprenorphine and naloxone exposure was approximately similar between the SL tablet and film formulation, however, both dosage forms are not considered bioequivalent across the dose range examined (2/0.5 mg to 12/3 mg). The clinical implications of the tendency for higher buprenorphine exposure after Suboxone film administration when switching between both dosage forms are adequately reflected in the SmPC.

The time for oromucosal disintegration appears to be only modestly shorter for the films as compared to SL tablets. Along the same lines, it is questionable whether the films present relevant advantages in terms of removability of administered doses after supervised dosing. The ability of patients to remove administered Suboxone films appears to be mainly driven by moistening the mouth prior to dosing and the number of film units that is administered at once. The requirement to moisten the mouth prior to film administration and the maximum number of two simultaneously applied film units are addressed in the product particulars.

2.5. Clinical efficacy

Suboxone films are intended for use in the treatment of opioid dependence over the same dose range as Suboxone sublingual tablets. No new indication for Suboxone films is being sought over that previously approved for Suboxone SL tablets, and no new efficacy studies are included as part of this application.

The safety and efficacy data that supported the Suboxone sublingual tablet registration are considered to support this application for Suboxone films. The objective of the clinical development programme for Suboxone films was to generate comparative PK data for the tablet and film demonstrating a lack of substantial differences between the formulations (and thus no expected clinically relevant bearing on

therapeutic outcome), in order to connect the established safety and efficacy of Suboxone sublingual tablets to this application for Suboxone films.

2.5.1. Dose response study(ies)

N/A

2.5.2. Main study(ies)

On top of the PK studies presented above, two phase II studies were conducted in support of the Suboxone SL film strip MAA.

A Phase 2, Multi-Center, Open-Label Study to Assess the Safety and Tolerability of a Buprenorphine / Naloxone Film Strip Administered by the Sublingual and Buccal Routes (Protocol Number RB-US-07-0001)

The objective of the open-label study RB-US-07-0001 was to assess the safety and tolerability in opioid dependent patients of buprenorphine and naloxone soluble film administered either sublingually or bucally daily for 12 weeks with particular emphasis on adverse events on the oral mucosa. Prior to the study, subjects had been taking Suboxone (buprenorphine and naloxone) sublingual tablets at a daily dose of 4 to 32 mg of buprenorphine. The study drug was administered in a dose equivalent to the daily sublingual tablet dose for twelve weeks.

Although an actual efficacy assessment was not included in the protocol, total daily dose adjustment (from tablets to soluble film) was summarized and the adequacy of total daily dose transition was explored to address FDA concerns expressed by the Agency at the 24 June 2008 pre-NDA meeting.

Total Daily Dose Adjustments
Mean total daily dose administered sublingually was 14.6 mg/day at baseline and 15.8 mg/day at last visit, and mean total daily dose administered buccally was 14.8 mg/day at baseline and 15.9 mg/day at last visit.

Table Change in Total Daily Dose (mg/day) from Baseline by Visit

	Buprenorphine and Naloxone Soluble Film						
	Visit 3 (Week 2)	Visit 4 (Week 4)	Visit 5 (Week 6)	Visit 6 (Week 8)	Visit 7 (Week 10)	Visit 8 (Week 12)	Visit 9 (Week 13)
Sublingual							
n	176	164	157	151	141	128	159
Mean (SD)	0 (0.15)	0.4 (1.83)	0.8 (2.44)	1.2 (2.84)	1.4 (3.18)	1.4 (3.09)	1.3 (2.98)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Range	0 – 2	-4 – 12	-4 – 12	-4 – 12	-8 – 12	-4 – 12	-4 – 12
Buccal							
n	170	165	158	151	145	135	170
Mean (SD)	0 (0.0)	0.2 (1.46)	0.4 (2.32)	1.0 (2.96)	1.4 (3.42)	1.4 (3.64)	1.2 (3.41)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Range	0	-8 – 8	-8 – 8	-8 – 12	-8 – 12	-8 – 16	-8 – 16

Abbreviations: SD = standard deviation

Data derived from Section 14, Statistical Table 20.1.

Three percent of subjects or less had their total daily dose decreased from baseline to any study treatment visits in either treatment groups. Increases in total daily dose from baseline were observed in the sublingual group cumulatively at Visits 3 to 9 in 1%, 7%, 13%, 17%, 21%, 20%, and 20% of subjects, respectively. Increases in total daily dose from baseline were observed in the buccal group cumulatively at Visits 4 to 9 in 4%, 10%, 16%, 22%, 21%, and 19% of subjects, respectively. Thirty-two subjects in each treatment group, corresponding to 20.1% and 18.8% of sublingually-treated and buccally-treated subjects, respectively, attending Visit 9, had their total daily dose increased at any point during the study.

Table Number (%) of Subjects with Changes from Baseline in Total Daily Dose

	Buprenorphine and Naloxone Soluble Film Number (%) of Subjects						
	Visit3 (Week 2)	Visit 4 (Week 4)	Visit 5 (Week 6)	Visit 6 (Week 8)	Visit 7 (Week 10)	Visit 8 (Week 12)	Visit 9 (Week 13)
Sublingual							
n	176	164	157	151	141	128	159
Decrease	0	2 (1.2)	2 (1.3)	2 (1.3)	3 (2.1)	2 (1.6)	2 (1.3)
No change	175 (99.4)	150 (91.5)	136 (86.0)	123 (81.5)	108 (76.6)	100 (78.1)	125 (78.6)
Increase	1 (0.6)	12 (7.3)	20 (12.7)	26 (17.2)	30 (21.3)	26 (20.3)	32 (20.1)
Buccal							
n	170	165	158	151	145	135	170
Decrease	0	1 (0.6)	3 (1.9)	2 (1.3)	3 (2.1)	4 (3.0)	5 (2.9)
No change	170 (100)	157 (95.2)	140 (88.6)	125 (82.8)	110 (75.9)	103 (76.3)	133 (78.2)
Increase	0	7 (4.2)	15 (9.5)	24 (15.9)	32 (22.1)	28 (20.7)	32 (18.8)

Data derived from Section 14, Statistical Table 22.1.

Induction of Opioid-Dependent Individuals onto Buprenorphine and Buprenorphine / Naloxone
(Protocol No. RB-US-07-0002)

The purpose of the double-blind phase II study RB-US-07-0002 was to compare the presence, degree, time course and profile of opioid withdrawal symptoms associated with induction onto buprenorphine soluble films and buprenorphine/naloxone soluble films in persons with active opioid dependence. The primary outcome measure was the severity of withdrawal symptoms measured using the Clinical Opioid Withdrawal Scale COWS.

Subjects were maintained on morphine for the first six days (window of 5 to 8 days) after admission to the clinical unit. On the day prior to the first day of soluble film administration, the 17:00 and 22:00 hours doses of morphine were switched to blind doses of placebo, to increase the likelihood that the subject experienced mild to moderate opioid withdrawal the next morning (i.e., prior to the first dose of soluble films). No morphine was to be administered once soluble film dosing commenced.

All subjects were to receive a minimum dose of 12 mg buprenorphine (i.e., 12 mg buprenorphine soluble films or 12/3 mg buprenorphine/naloxone soluble films) on the first day of soluble film administration and 16 mg on the second day of induction. Thereafter, a flexible dosing scheme was used and doses could have been increased as high as 24 mg of buprenorphine as appropriate for the rest of the double-blind period (from day 3 to day 5). On the first day of soluble film administration, soluble films were administered as divided doses given as 4 mg buprenorphine or 4/1 mg buprenorphine/naloxone dose at 09:00, 11:00, and 20:00 hours (i.e., the total daily dosage on the first day of soluble film dosing was 12 mg buprenorphine or 12/3 mg buprenorphine/naloxone). On subsequent days, soluble films were administered at 09:00 each day.

The primary outcome measure was COWS scores, specifically, the difference between the maximum post soluble film administration COWS score (during the 23.5 hour period after the first day's soluble films administration) and the baseline score (the score obtained 30 minutes prior to administration of soluble films on the first day of administration of soluble films).

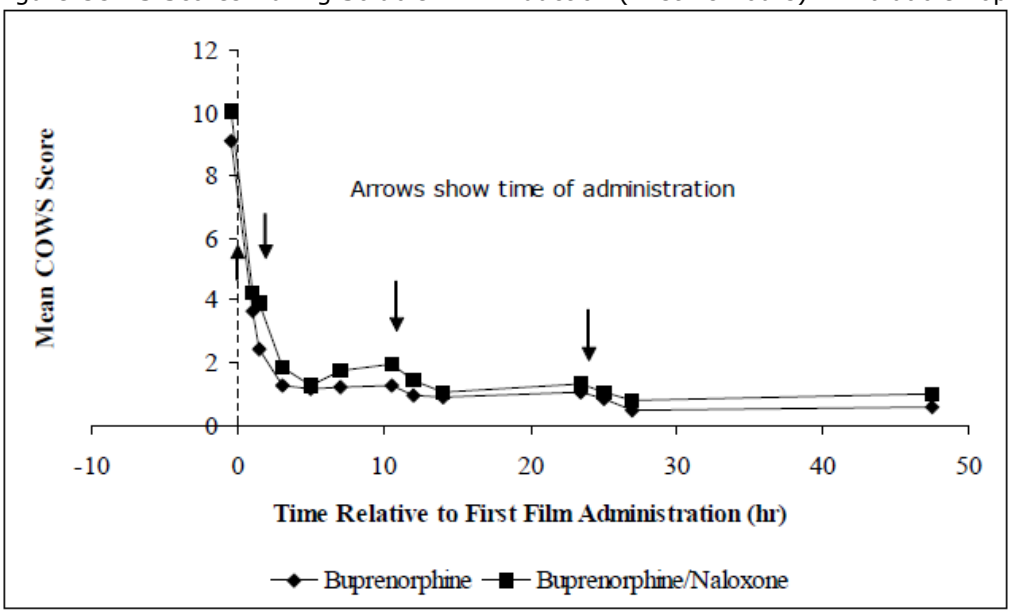
As shown in the Table below, there were no significant differences between the two groups in baseline or peak scores; however, there was a statistically significant reduction ($p<0.0001$) between the peak scores and those at baseline.

Table Comparison of Baseline and Peak COWS Scores During Soluble Film Induction (first 23.5 hours of Soluble Film Administration) – Evaluable Population

	Group A vs Group B		**Baseline vs Peak**		**Interaction**	
	F (df=1,32)	**p**	**F (df=1,32)**	**p**	**F (df=1,32)**	**p**
	0.94	0.339	23.96	<0.0001	0.09	0.767
	Baseline		**Peak**		**Baseline Versus Peak**	
	Mean	**SD**	**Mean**	**SD**	**t**	**p-value**
Buprenorphine N=18	9.1	5.5	4.2	2.4	3.79	0.001
Buprenorphine / Naloxone N=16	10.1	6.4	5.7	3.2	3.16	0.004

Although peak scores imply an increase, peak actually refers to the highest score in the assessment period, which was lower than that score during baseline. This is best depicted in the Figure below.

Figure COWS Scores During Soluble Film Induction (First 48 hours) – Evaluable Population



The baseline mean (SD) COWS scores for subjects in the buprenorphine group was 9.1 (5.5) and for that of the buprenorphine/naloxone group of 10.4 (6.4). Scores of 5 to 12 are considered mild withdrawal; however, some subjects were experiencing moderate levels of withdrawal (scores of 13 to 24). The mean peak scores (SD) in the 23.5 hr period after soluble film administration were 4.2 (2.4) and 5.7 (3.2) for the buprenorphine and buprenorphine/naloxone groups, respectively.

As can be seen in the Figure above, there was a rapid decline in COWS scores by the time of the first measurement at 1 hour post administration in both groups, which reached its lowest level by 4 hours post-dose and stayed low for the duration of the induction period (48 hours).

Clinical studies in special populations

N/A

Supportive study(ies)

Apart from the two phase II trials (RB-US-07-0001 and RB-US-07-0002, conducted in 2008) discussed above, the buprenorphine / naloxone films were used for treatment induction in patients with opioid use disorder (OUD) in two more recent trials (RB-US-13-0001, RB-US-13-0003). These were conducted to support the MAA for RBP-6000, a subcutaneous buprenorphine depot injection, at a time when the Suboxone films were already approved and marketed in the US. Studies RB-US-13-0001 and RB-US-13-0003 were not discussed in Module 2.7.3 and are mentioned here for the sake of completeness, only.

2.5.3. Discussion on clinical efficacy

Although formally categorized as safety studies, both study RB-US-07-0001 (subsequently referred to as study 01) and study RB-US-07-0002 (subsequently referred to as study 02) potentially cover important efficacy aspects of the new film strip dosage form, namely dose stabilization after 1:1 dose equivalent switch from SL tablets to SL films and the occurrence of opioid withdrawal symptoms.

After consistently higher buprenorphine absorption from the films as compared to the SL tablets was found during the PK studies, the issue of dose stability during treatment induction and maintenance therapy is of crucial importance.

The focus of study RB-US-07-0001 was placed upon monitoring local tolerability. As pointed out by the Applicant, actual efficacy assessment was originally not planned according to the study protocol. After the FDA expressed concerns at the pre-NDA meeting, total daily dose (TDD) adjustment summarization and TDD transition exploration was included.

As known from bioequivalence studies, absorption from the SL films as compared to the SL tablets was increased (single dose studies 20-250-SA and 20-273-SA: Cmax increase by 21.6 to 27.8%, AUClast increase by 16.4 to 20.1%). Hence, it could therefore be expected that lower dose of the SL films as compared to the SL tablets were required. The general concern, however, is that opioid dependent patients are less likely to voluntarily ask for dose reduction, but instead are expected to favour any chance for receiving higher doses. In this context, the meaningfulness of assessing total daily dose adjustment is limited by the outpatient open-label design of the study with apparent lack of objective opioid withdrawal assessment.

About one third of recruited subjects did not complete the study. The mean time to discontinuation (SL arm: 61 days, buccal arm: 57 days) was late, almost shortly before finalisation of the 12-week treatment period. Hence, study discontinuation is unlikely to be directly related to transition from SL tablets to buprenorphine / naloxone films. In general, high study discontinuation is frequently observed in trials with subjects suffering from opioid dependence. The actual numbers are difficult to interpret due to the open label design of the study and the lack of a comparator arm (e.g. subjects remaining on SL tablets).

More than 60% of patients took their last dose of Suboxone on the same day as their first dose of study drug, hence received a double dose of buprenorphine on the first day of the treatment period. Under these circumstances, any evaluation of adequacy of transition from SL tablets to films appears meaningless.

Urine drug screen results were not included in this report. However, when assessing TDD adjustments after the switch from SL tablets to the films, it is of crucial importance to rule out any overlapping opioid consumption. This was not guaranteed by the outpatient design of the study and the lack of systematic recording (or ban) of concomitant illicit opioid use. It is reminded that study RB-US-07-0001 was mainly and originally designed as a safety study to monitor local tolerability. Yet, the above mentioned design-related shortcomings in the way of measuring TDD adjustments as an efficacy parameter greatly compromise data interpretability.

The baseline dose was almost maintained over the 12-wk treatment period in both arms. The mean dose was increased by 1-2 mg buprenorphine per arm. There was no difference between sublingual and buccal administration in this regard. As outlined above, however, data are to be interpreted with caution due to the open label design and the lack of confirming the necessity for dose increments by objective measures (COWS).

Apart from mean adjustments in total daily dose, which were low over the 12-wk treatment period in terms of the absolute buprenorphine dose, about 20% of subjects had dose increases at any point during the study. The percentage of subjects with dose reductions was considerably smaller (1-3%). Like already observed for adjustments in total daily buprenorphine dose, the difference between the SL and buccal arm was also little in terms of percentage of subjects with dose increases resp. decreases.

Based on PK data, which demonstrated higher systemic buprenorphine exposure for the film formulation as compared to the SL tablets, one could have expected rather a tendency for dose decreases after the switch from SL tablets to the films. In the particular target population of opioid dependent subjects, however, these results do not surprise, since subjects with substance use disorders are considered less likely to voluntarily ask for dose reduction, but instead are expected to favour any chance for receiving higher doses. Furthermore, additional non-study opioid consumption, which may greatly impact on buprenorphine dose requirements, was neither categorically banned (by the outpatient design) nor systematically assessed (no systematic analysis of urine drug screens). No objective data on dose adequacy (e.g. COWS) are available.

In essence, it is concluded that interpretability of efficacy data is greatly compromised by design-related shortcomings of study RB-US-07-0001, i.e. open-label, outpatient design without systematic ban / assessment of additional opioid consumption from non-study sources and insufficient demonstration of dose adequacy at baseline and during treatment.

Nonetheless, study RB-US-07-0001 demonstrates that the majority of opioid dependent subjects maintained on SL tablets could be switched to the film formulation and that about two thirds of included subjects completed the entire 12-wk treatment period receiving either sublingual or buccal buprenorphine / naloxone films.

Within the context of the present MAA, it is considered that study RB-US-07-0001 is supportive. Approvability of the intended line extension mainly depends on demonstration of similarity of the PK profiles between the established SL tablets and the newly developed film formulations.

In study RB-US-07-0002 the focus is upon the potential of the new SL films to provoke opioid withdrawal symptoms due to the naloxone component. No comparison is made between SL tablets and SL films, but between mono-entity buprenorphine films vs fixed-combination buprenorphine/naloxone films. The mono-entity buprenorphine films are not marketed.

The buprenorphine / buprenorphine/naloxone film dose was not individually titrated. During the two-day induction period fixed doses of buprenorphine were administered (12 mg on day 1 and 16 mg on day 2). This corresponds to the proposed SmPC, which recommends a starting dose in adults of Suboxone 4/1 mg films, which can be repeated up to twice to minimise undue withdrawal symptoms and retain the patient in treatment.

After the comparative bioavailability studies showed that the naloxone exposure after the SL film administration was higher than after Suboxone tablet administration, the question arises whether the amount of naloxone delivered could have an impact on the ability of patients of successful transition from illicit drug use to maintenance treatment with buprenorphine. Study RB-US-07-0002 does not fully address this question. The study focused on group mean measures of withdrawal on the Clinical Opiate Withdrawal Scale (COWS) as an efficacy measure for buprenorphine and buprenorphine/naloxone films. In the context of this line extension MAA it would have been preferable, however, to examine whether any differential naloxone level would translate into decreased likelihood of a patient completing induction and becoming successfully stabilized on a dose of buprenorphine/naloxone (as a [non-inferiority] comparison between the SL tablets and the SL films). Study 02 does not directly answer the question, however, provides some insight into the

experience of patients transitioning from a full agonist (morphine) to the buprenorphine/naloxone combination strip.

All included subjects were heroin users with different patterns of additional illicit drug consumption. Patients were transfered to subcutaneous morphine injections of 30 mg four times daily. Baseline opioid withdrawal scores were recorded just before the start of the film treatment. On the day before the first film administration the last two s.c. morphine administrations (at 17.00 and 22.00 hours) were replaced by placebo in order to increase the likelihood of withdrawal. However, baseline withdrawal scores were still rather low indicating mild withdrawal (COWS: buprenorphine 9.1, bup/nal 10.1).

On the first day of induction the buprenorphine dose was divided into three parts of 4 mg given at 9.00, 11.00 and 20.00 hours. The good and rapid efficacy of buprenorphine and / buprenorphine/naloxone is demonstrated by the fact that even with the first 4 mg dose baseline COWS scores (about 9-10) are about halved (COWS score about 4) within two hours post administration. With the second 4mg dose, given two hours after the first dose, a further halving of the withdrawal symptoms (COWS score about 2) is achieved within about further two hours in both treatment arms.

For the rest of the 48 hour induction period COWS scores remain low (below 5) for both treatment groups, not indicating relevant withdrawal. A slight tendency for higher withdrawal scores is noted for the buprenorphine/naloxone fixed combination as compared to the buprenorphine films. However, the difference is minimal and considered not to be clinically relevant.

The study met the primary objective by showing that there was a statistically significant reduction ($p<0.0001$) between the peak scores and those at baseline for both groups. However, no comparison between the two groups was planned. The non-significant difference between the groups does not imply that there is no difference between the groups. In order to show in a confirmatory way that withdrawal symptoms under buprenorphine/naloxone are not relevantly worse than under buprenorphine alone, it would have been necessary to pre-specify a non-inferiority test and a non-inferiority margin.

Overall, the comparison of mean COWS scores over time for the two groups suggests that the naloxone component in the newly developed film strip formulation did not lead to an increase in opioid withdrawal symptoms as compared to buprenorphine films during the first days of treatment induction after stabilization and standardization with subcutaneous morphine. However, there is no statistical confirmation of this hypothesis. From a principle perspective of the present line extension procedure, a comparison between the established SL tablets and the newly developed films would have been more meaningful.

Within the context of the present MAA, it is considered that study RB-US-07-0002 is supportive.

2.5.4. Conclusions on the clinical efficacy

Based on similar PK profiles between the SL tablet and film formulation, no efficacy studies in support of the new film strip formulation were conducted. The demonstration of efficacy for the Suboxone SL films relies upon the known efficacy of buprenorphine and naloxone SL tablets combinations for the treatment of opioid dependence, which is acceptable.

In terms of efficacy / safety two supportive phase II studies were submitted that originally were designed as safety studies. The adequacy of total daily dose transition (from SL tablets to films) was explored in study RB-US-07-0001 to address FDA concerns expressed by the FDA at the 24 June 2008 preNDA meeting.

In essence, it is concluded that interpretability of efficacy data is greatly compromised by design-related shortcomings of study RB-US-07-0001, i.e. open-label, outpatient design without systematic ban of additional opioid consumption from non-study sources and insufficient demonstration of dose adequacy at baseline and during treatment (e.g. by monitoring withdrawal [COWS]). Nonetheless, study RB-US-07-0001 is considered to contribute supportive clinical data to the present MAA. About two thirds of recruited patients completed the study, thereby showing that the majority of patients previously maintained on Suboxone SL tablets can successfully be switched to the film formulation.

Study RB-US-07-0002 was a small single center 34-subject inpatient, double-blind study intended to demonstrate that neither buprenorphine nor buprenorphine/naloxone soluble film formulation would precipitate an opioid withdrawal syndrome during initiation of treatment. Heroin users were initially stabilized on s.c.morphine (30 mg four times daily) and then underwent challenge sessions with naloxone and placebo to ensure that subjects are sensitive to opioid withdrawal. Subjects who met the criteria to continue in the study were randomized to treatment with buprenorphine soluble films or buprenorphine/naloxone films. Treatment with buprenorphine was initiated with three divided 4 mg doses, totalling 12 mg the first day, with subsequent dosing of 16 mg-24 mg/day as a single daily dose for four additional days (Day 1+2 Induction, Day 3-5 Post-Induction). Subjects were evaluated for the severity of withdrawal symptoms using physiological and behavioural measures (Clinical Opioid Withdrawal Scale COWS, 100 mm VAS Scale on subjective Drug Effects, Pupil Diameter).

The study met the primary objective by showing that there was a statistically significant reduction ($p<0.0001$) between the peak scores during the 23.5 hour period after treatment initiation and those at baseline for both groups.

Within the context of the present line extension procedure, a comparison between the established SL tablets and the newly developed films would have been more meaningful than comparing mono-entity buprenorphine with the fixed combination of buprenorphine / naloxone. Overall, it is therefore concluded that study 02 did not directly answer the question whether buprenorphine / naloxone SL tablets and SL films demonstrate a similar likelihood of successful treatment induction in illicit drug users. However, it did provide some insight into the experience of patients transitioning from a full agonist (morphine) to the buprenorphine/naloxone combination film strip.

Overall, study RB-US-07-0002 is therefore considered to contribute supportive clinical data to the overall data package for the new film formulation, that mainly relies on PK comparison with the marketed SL tablets.

2.6. Clinical safety

Patient exposure

The characterisation of the safety profile of Suboxone® sublingual (SL) film (buprenorphine/naloxone in a 4:1 ratio) is based on evaluations in the following:

- Nineteen Phase I pharmacokinetic (PK) studies.

- Two Phase II studies: Study RB-US-07-0001, a randomised, open-label safety and tolerability study of buprenorphine/naloxone SL in subjects with a history of opioid dependence and Study RB-US-07-0002, a randomised dose induction study.
- Run-in data from 2 Phase III studies of the RBP-6000 clinical development program: Studies RB-US-13-0001 and RB-US-13-0003. The study design of both Phase III studies employed an open-label run-in phase, where subjects enrolled in the trial received Suboxone SL film for 14 days before they were assigned to receive different doses of RBP-6000. These data are presented in this safety summary.
- Comparison of adverse event (AE) profiles of buprenorphine/naloxone SL film with Suboxone SL tablets.
- Post-marketing data and literature results.

The 19 PK study population, the integrated phase II study population, and subjects participating in the Run-In Phases in studies RB-US-13-0001 and RB-US-13-0003 were assigned to three subject groupings for which safety data were summarized.

Adverse events

Common Treatment emergent adverse events (TEAE)

Table Summary of Treatment-emergent Events in ≥2% of Subjects in Any Treatment Group by System Organ Class and Preferred Terms in Healthy Volunteer Studies[a]

System Organ Class[c] Preferred term	Treatment Group Number (%) of Subjects[b]			
	SUBUTEX SL tablet N=206	Buprenorphine SL film N=351	SUBOXONE SL tablet N=313	Buprenorphine/Naloxone SL film N=459
At least 1 adverse event[d]	**88 (42.7%)**	**233 (66.4%)**	**150 (47.9%)**	**301 (65.6%)**
Gastrointestinal disorders	**57 (27.7%)**	**171 (48.7%)**	**108 (34.5%)**	**235 (51.2%)**
Nausea	40 (19.4%)	136 (38.7%)	74 (23.6%)	184 (40.1%)
Vomiting	19 (9.2%)	64 (18.2%)	19 (6.1%)	66 (14.4%)
Abdominal pain	14 (6.8%)	42 (12.0%)	24 (7.7%)	62 (13.5%)
Constipation	10 (4.9%)	27 (7.7%)	15 (4.8%)	49 (10.7%)
Diarrhoea	7 (3.4%)	25 (7.1%)	5 (1.6%)	18 (3.9%)
Dyspepsia	3 (1.5%)	8 (2.3%)	6 (1.9%)	12 (2.6%)
Dry mouth	1 (0.5%)	12 (3.4%)	1 (0.3%)	7 (1.5%)
Paraesthesia oral	1 (0.5%)	7 (2.0%)	2 (0.6%)	6 (1.3%)
Nervous system disorders	**56 (27.2%)**	**150 (42.7%)**	**63 (20.1%)**	**188 (41.0%)**
Headache	27 (13.1%)	82 (23.4%)	36 (11.5%)	103 (22.4%)
Dizziness	19 (9.2%)	77 (21.9%)	24 (7.7%)	84 (18.3%)
Somnolence	16 (7.8%)	52 (14.8%)	12 (3.8%)	67 (14.6%)
General disorders and administration site conditions	**8 (3.9%)**	**52 (14.8%)**	**14 (4.5%)**	**49 (10.7%)**
Fatigue	3 (1.5%)	23 (6.6%)	7 (2.2%)	26 (5.7%)
Asthenia	4 (1.9%)	13 (3.7%)	0 (0.0%)	7 (1.5%)
Psychiatric Disorders	**6 (2.9%)**	**37 (10.5%)**	**7 (2.2%)**	**35 (7.6%)**
Euphoric mood	1 (0.5%)	12 (3.4%)	4 (1.3%)	11 (2.4%)
Anxiety	1 (0.5%)	10 (2.8%)	1 (0.3%)	6 (1.3%)
Confusional state	2 (1.0%)	3 (0.9%)	2 (0.6%)	9 (2.0%)
Infections and Infestations	**4 (1.9%)**	**20 (5.7%)**	**9 (2.9%)**	**21 (4.6%)**
Pharyngitis	1 (0.5%)	8 (2.3%)	4 (1.3%)	6 (1.3%)
Upper respiratory tract infection	1 (0.5%)	8 (2.3%)	3 (1.0%)	6 (1.3%)
Metabolism and nutrition disorders	**2 (1.0%)**	**10 (2.8%)**	**4 (1.3%)**	**12 (2.6%)**
Anorexia	2 (1.0%)	9 (2.6%)	4 (1.3%)	12 (2.6%)
Reproductive system and breast disorders	**1 (0.5%)**	**6 (1.7%)**	**5 (1.6%)**	**14 (3.1%)**
Dysmenorrhoea	0 (0.0%)	3 (0.9%)	1 (0.3%)	9 (2.0%)

[a] Includes Studies 20-A70-AU, 20-A71-AU, 20-A72-AU, 20-197-SA, 20-A78-AU, 20-250-SA, 20-272-SA, 20-273-SA, 20-277-SA, 20-276-SA, 20-B17-AU, 20-B20-AU, 20-A79-AU, 20-A90-AU, 20-290-SA, 20-291-SA, 20-293-SA, 20-B24-AU and 1003395.

[b] Because these are crossover studies that compared different treatments and routes of administration, the number of subjects exposed to each study drug formulation exceeds the total number of subjects in the studies.

[c] Adverse events were coded using MedDRA version 11.0 terminology.

[d] Every event is counted only once within subject, treatment group, SOC and PT. Table is organised by decreasing frequency of SOC, then by PT overall.

Data derived from Module 5.3.5.3, Statistical Table 14.7.1.1.

It must be noted that to improve the tolerability of buprenorphine in opioid-naïve and/or opioid non-dependent individuals, a 50 or 100-mg dose of naltrexone, an opioid antagonist, was administered at approximately 12 hours and 1 hour prior to each study treatment and a 50-mg dose was administered at approximately 24 hours or at approximately 12 and 24 hours after each study treatment. Pre-treatment with naltrexone can block AEs in opioid-naïve healthy subjects, or naïve subjects can experience AEs, such as nausea, in response to the naltrexone pre-treatment. Therefore, the potential exists that some TEAEs may be related to naltrexone pre-treatment, whether administered before or after buprenorphine or buprenorphine/naloxone.

Table Treatment-Emergent Adverse Events Reported by at Least 2% of Subjects Overall Treated with Buprenorphine/Naloxone SL film (Integrated Studies RB-US-07-0001 and RB-US- 07-0002)

System Organ Class[a] Preferred Term	SL film Treatment Group Number (%) of Subjects		
	Buprenorphine[b] N=20	Buprenorphine/ Naloxone[c] N=400	Total N=420
At Least 1 TEAE	**19 (95.0%)**	**134 (33.5%)**	**153 (36.4%)**
Gastrointestinal Disorders	**10 (50.0%)**	**53 (13.3%)**	**63 (15.0%)**
Stomach discomfort	7 (35.0%)	8 (2.0%)	15 (3.6%)
Nausea	3 (15.0%)	10 (2.5%)	13 (3.1%)
Oral mucosa erythema	0 (0.0%)	8 (2.0%)	8 (1.9%)
Nervous System	**10 (50.0%)**	**23 (5.8%)**	**33 (7.9%)**
Headache	6 (30.0%)	11 (2.8%)	17 (4.0%)
Restlessness	4 (20.0%)	8 (2.0%)	12 (2.9%)
Psychiatric Disorders	**10 (50.0%)**	**19 (4.8%)**	**29 (6.9%)**
Anxiety	6 (30.0%)	9 (2.3%)	15 (3.6%)

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

Note: Due to the small sample size in the buprenorphine SL film group (n=20), this table is limited to TEAEs reported by at least 2% of subjects treated with buprenorphine/naloxone SL film.

[a] Adverse events were coded using MedDRA version 11.0 terminology. Every event is counted only once within subject, each treatment group, SOC and PT. Sorting is done by decreasing frequency of SOC, then by PT, in the Total column.

[b] SL administration.

[c] Both routes of administration, buccal and sublingual.

Data derived from Module 5.3.5.3, Statistical Table 14.7.1.4.

Adverse Events of Special Interest (AESI)

Adverse events of special interest that occurred during the Phase I (PK) studies are summarised in the Table below. The most frequently reported AESIs in subjects treated with buprenorphine/naloxone SL film were paraesthesia oral (6 subjects, 1.3%), conjunctivitis (6 subjects, 1.3%), and chest pain (5 subjects, 1.1%). Paraesthesia oral was also reported in 7 (2.0%) subjects treated with buprenorphine SL film compared with 1 (0.5%) subject treated with SUBUTEX SL tablets and 2 (0.6%) subjects treated with SUBOXONE SL tablets.

Table Summary of Adverse Events of Special Interest by System Organ Class and Preferred Terms in Healthy Volunteer Studies [a]

System Organ Class[c,d] Preferred term	Treatment Group Number (%) of Subjects[b]			
	SUBUTEX SL tablet N=206	Buprenorphine SL film N=351	SUBOXONE SL tablet N=313	Buprenorphine/ Naloxone SL film N=459
At least 1 AE of special interest[c,d]	**3 (1.5%)**	**16 (4.6%)**	**10 (3.2%)**	**31 (6.8%)**
Gastrointestinal Disorders	**1 (0.5%)**	**12 (3.4%)**	**5 (1.6%)**	**13 (2.8%)**
Paraesthesia oral	1 (0.5%)	7 (2.0%)	2 (0.6%)	6 (1.3%)
Toothache	0 (0.0%)	2 (0.6%)	2 (0.6%)	1 (0.2%)
Hypoaesthesia oral	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.4%)
Salivary hypersecretion	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Aphthous stomatitis	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Cheilitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Gingivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Oral pain	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Saliva altered	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous System Disorders	**1 (0.5%)**	**1 (0.3%)**	**3 (1.0%)**	**4 (0.9%)**
Dysgeusia	1 (0.5%)	1 (0.3%)	3 (1.0%)	4 (0.9%)
Eye Disorders	0 (0.0%)	1 (0.3%)	0 (0.0%)	6 (1.3%)
Conjunctivitis	0 (0.0%)	1 (0.3%)	0 (0.0%)	6 (1.3%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**0 (0.0%)**	**1 (0.3%)**	**5 (1.1%)**
Chest pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	5 (1.1%)
Cardiac Disorders	1 (0.5%)	2 (0.6%)	1 (0.3%)	1 (0.2%)
Palpitations	1 (0.5%)	2 (0.6%)	1 (0.3%)	1 (0.2%)
Infections and Infestations	**0 (0.0%)**	**1 (0.3%)**	**0 (0.0%)**	**4 (0.9%)**
Oral herpes	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
Folliculitis	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class.
Note: Includes analysis of clinical chemistries that are affected by hepatic function: ALT, AST, total bilirubin, creatinine and alkaline phosphatase.

[a] Includes Studies 20-A70-AU, 20-A71-AU, 20-A72-AU, 20-197-SA, 20-A78-AU, 20-250-SA, 20-272-SA, 20-273-SA, 20-277-SA, 20-276-SA, 20-B17-AU, 20-B20-AU, 20-A79-AU, 20-A90-AU, 20-290-SA, 20-291-SA, 20-293-SA, 20-B24-AU and 1003395.

[b] Because these were crossover studies that compared different treatments and routes of administration, the number of subjects exposed to each drug formulation exceeds the total number of subjects in the studies.

[c] Adverse events were coded using MedDRA version 11.0 terminology.

[d] Every event is counted only once within subject, treatment group, SOC and PT. This table is organised by decreasing frequency of SOC, then by PT overall.

Data derived from Module 5.3.5.3, Statistical Table 14.7.13.1.

Adverse events of special interest that occurred during the Phase II studies are summarised in the Table below. Twenty-eight (6.7%) of 420 opioid-dependent subjects treated with either buprenorphine (2/20, 10.0%) or buprenorphine/naloxone (26/400, 6.5%) SL film had treatment-emergent AESIs reported.

The most frequently reported AESIs in the 400 subjects treated with buprenorphine/naloxone film (administered sublingually or buccally) were oral mucosal erythema (8 subjects, 2.0%), toothache (7 subjects, 1.8%), hypoesthesia oral (3 subjects, 0.8%), and cellulitis (2 subjects, 0.5%). Oral pain, paraesthesia oral, folliculitis, fungal skin infection, palpitations, and liver function test abnormal were reported in 1 (0.3%) buprenorphine/naloxone SL film subject each.

Table Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term (Integrated Studies RB-US-07-0001 and RB-US-07-0002)

System Organ Class[a] Preferred term	SL film Treatment Group Number (%) of Subjects[b]		
	Buprenorphine[c] N=20	Buprenorphine / Naloxone[d] N=400	Total N=420
At least 1 AESI	**2 (10.0%)**	**26 (6.5%)**	**28 (6.7%)**
Gastrointestinal Disorders	**1 (5.0%)**	**20 (5.0%)**	**21 (5.0%)**
Oral mucosal erythema	0 (0.0%)	8 (2.0%)	8 (1.9%)
Toothache	0 (0.0%)	7 (1.8%)	7 (1.7%)
Hypoaesthesia oral	0 (0.0%)	3 (0.8%)	3 (0.7%)
Gingival blister	1 (5.0%)	0 (0.0%)	1 (0.2%)
Oral pain	0 (0.0%)	1 (0.3%)	1 (0.2%)
Paraesthesia oral	0 (0.0%)	1 (0.3%)	1 (0.2%)
Infections and Infestations	**0 (0.0%)**	**4 (1.0%)**	**4 (1.0%)**
Cellulitis	0 (0.0%)	2 (0.5%)	2 (0.5%)
Folliculitis	0 (0.0%)	1 (0.3%)	1 (0.2%)
Fungal skin infection	0 (0.0%)	1 (0.3%)	1 (0.2%)
Cardiac Disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Palpitations	0 (0.0%)	1 (0.3%)	1 (0.2%)
Investigations	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Liver function test abnormal	0 (0.0%)	1 (0.3%)	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (5.0%)**	**0 (0.0%)**	**1 (0.2%)**
Chest pain	1 (5.0%)	0 (0.0%)	1 (0.2%)

Abbreviations: AESI=adverse event of special interest; ALT=alanine transaminase; AST=aspartate transaminase; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class.
Includes analysis on clinical chemistries that are affected by hepatic function (ALT, AST, total bilirubin, creatinine and alkaline phosphatase).

[a] Adverse events were coded using MedDRA version 11.0 terminology.

[b] Every event is counted only once within subject, each treatment group, SOC class and PT. This table is organised by decreasing frequency of SOC, then by PT, in the total subjects column.

[c] Sublingually administered.

[d] Sublingually or buccally administered.

Data derived from Module 5.3.5.3, Statistical Table 14.7.13.4.

Serious adverse event/deaths/other significant events

Serious AE

Apart from one SAE (acute optic neuritis of the right eye) that was reported during Study 20-277-SA, no other SAEs were reported during the 19 Phase I studies.

No SAEs were reported during Study RB-US-07-0002. All of the SAEs in this section were reported in RB-US-07-0001.

A total of 7 SAEs were reported by 6 (1.4%) of the 420 subjects; none of the SAEs were considered related to study drug. All SAEs were reported by subjects treated with buprenorphine/naloxone film (SL or buccal) during Study RB-US-07-0001. One subject (RB-US-07-0001, Subject 333073) reported 2 SAEs (squamous cell carcinoma of the cervix and anaemia) after treatment with buprenorphine/naloxone film administered sublingually.

Serious adverse events occurring during the integrated Phase II studies (RB-US-07-0001 and RB-US 07-0002) are summarised in the Table below.

Table Serious Treatment-Emergent Adverse Events (Integrated Studies RB-US-07-0001 and RB-US-07-0002)

	SL film Treatment Group Number (%) of Subjects		
System Organ Class[a] Preferred term	**Buprenorphine N=20**	**Buprenorphine/ Naloxone[b] N=400**	**Total N=420**
At least 1 SAE	**0 (0.0%)**	**6 (1.5%)**	**6 (1.4%)**
Injury, Poisoning and Procedural Complications	**0 (0.0%)**	**2 (0.5%)**	**2 (0.5%)**
Road traffic accident	0 (0.0%)	1 (0.3%)	1 (0.2%)
Skin injury	0 (0.0%)	1 (0.3%)	1 (0.2%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0 (0.0%)**	**2 (0.5%)**	**2 (0.5%)**
Oesophageal carcinoma	0 (0.0%)	1 (0.3%)	1 (0.2%)
Squamous cell carcinoma of the cervix	0 (0.0%)	1 (0.3%)	1 (0.2%)
Blood and Lymphatic System Disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Anaemia	0 (0.0%)	1 (0.3%)	1 (0.2%)
Nervous System Disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Syncope vasovagal	0 (0.0%)	1 (0.3%)	1 (0.2%)
Renal and Urinary Disorders	**0 (0.0%)**	**1 (0.3%)**	**1 (0.2%)**
Nephrolithiasis	0 (0.0%)	1 (0.3%)	1 (0.2%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event; SOC=system organ class.

[a] Adverse events were coded using MedDRA version 11.0 terminology.

[b] Every event is counted once within subject, each treatment group, SOC and PT. The table is organised by decreasing frequency of SOC, then by PT in the total subjects column.

Data derived from Module 5.3.5.3, Statistical Table 14.7.16.4.

Deaths

No deaths were reported in the 19 Phase I (PK) studies in healthy subjects, in the Phase II studies (RB-US-07-0001 and RB-US-07-0002) or in the Suboxone SL film run-in phase of the Phase III studies of the RBP-6000 programme (RB-US-13-0001 and RB-US-13-0003).

Laboratory findings

There were no patterns indicative of a safety concern with respect to laboratory values and ECG data in healthy subjects.

Clinical laboratory (haematology, clinical chemistry, and clinical urinalysis) data were not collected in Study RB-US-07-0001 as the study was designed to primarily assess local tolerability, and as the safety of buprenorphine/naloxone has been well characterised by previously obtained data for the SL tablet formulation.

As concerns study RB-US-07-0002, for most parameters, there were no notable differences between baseline and post-test measurements, with the exception of ALT, AST, total cholesterol, and triglycerides (Table below).

Table Blood Chemistry (Study RB-US-07-0002)

	SL film Treatment Group					
	Buprenorphine (N=19)[a]			Buprenorphine/Naloxone (N=16)[a]		
	Baseline	Post-test	Change[b]	Baseline	Post-test	Change[b]
ALT; normal range 9-80 U/L (males) and 6-40 U/L (females)						
Mean	27.1	47.7	20.7	38.8	57.3	18.4
SD	22.15	41.26	29.67	40.13	58.01	41.24
Median	17.0	32.0	9.0	23.0	31.0	8.5
Min, Max	6, 91	9, 160	-8, 98	9, 160	9, 211	-48, 147
AST; normal range 10-40 U/L (males 20-49 years), 10-35 U/L (males ≥50 years), 10-30 U/L (females 20-44 years), and 10-35 U/L (females ≥45 years)						
Mean	27.8	35.5	7.7	34.6	41.7	7.1
SD	19.94	26.83	17.84	21.19	33.89	32.22
Median	20.0	26.0	3.0	24.0	28.5	2.5
Range	13, 98	12, 119	-12, 69	15, 71	15, 128	-46, 109
Total bilirubin; normal range 0.2-1.2 mg/dL						
Mean	0.59	0.53	-0.06	0.63	0.61	-0.03
SD	0.200	0.267	0.269	0.149	0.214	0.257
Median	0.60	0.50	-0.10	0.60	0.60	0.00
Range	0.3, 1.0	0.3, 1.2	-0.6, 0.6	0.4, 0.9	0.3, 1.0	-0.5, 0.4
Glucose; normal range 65-99 mg/dL						
Mean	90.3	97.9	7.6	90.9	94.3	3.3
SD	27.53	29.70	28.74	8.81	9.70	13.06
Median	90.0	93.0	2.0	90.0	92.5	4.5
Range	**13, 168**	41, 188	-48, 90	78, 110	81, 111	-25, 22
BUN; normal range 7-25 mg/dL						
Mean	11.6	14.5	2.9	14.0	14.1	0.1
SD	3.29	4.91	5.13	5.37	2.82	4.02
Median	12.0	14.0	2.0	13.0	14.5	1.0
Range	6, 18	10, 29	-4, 16	8, 31	9, 20	-11, 7
Creatinine; normal range 0.5-1.3 mg/dL (males) and 0.5-1.2 mg/dL (females)						
Mean	0.88	0.84	-0.04	0.88	0.91	0.03
SD	0.165	0.150	0.096	0.117	0.109	0.101
Median	0.80	0.80	0.00	0.90	0.90	0.00
Range	0.6, 1.2	0.6, 1.2	-0.3, 0.1	0.7, 1.1	0.8, 1.1	-0.1, 0.2
CO_2; normal range 21-33 mEq/L						
Mean	24.1	24.5	0.4	24.6	24.7	0.1
SD	2.78	3.44	4.51	1.89	3.40	2.52
Median	25.0	25.0	0.0	24.5	24.5	0.5
Range	16, 27	16, 29	-9, 13	20, 28	18, 31	-6, 4
Sodium; normal range 135-146 mmol/L						

Mean	141.2	139.9	-1.2	140.0	139.9	-0.1
SD	2.95	2.07	2.55	3.56	1.88	3.11
Median	141.0	140.0	-1.0	140.0	139.0	-0.5
Range	135, 148	136, 143	-7, 2	134, 146	136, 143	-5, 6
Potassium; normal range 3.5-5.3 mmol/L						
Mean	4.56	4.73	0.16	4.84	4.70	-0.14
SD	0.516	0.516	0.548	0.541	0.341	0.716
Median	4.50	4.60	0.10	4.65	4.70	0.00
Range	3.8, 6.1	4.0, 5.5	-0.9, 1.3	4.2, 6.2	4.1, 5.3	-1.4, 0.7
Calcium; normal range 8.6-10.2 mg/dL						
Mean	9.56	9.72	0.16	9.46	9.56	0.09
SD	0.378	0.246	0.382	0.301	0.426	0.343
Median	9.60	9.70	0.10	9.40	9.70	0.10
Range	9.0, 10.3	9.4, 10.4	-0.4, 0.8	8.8, 10.1	8.8, 10.2	-0.4, 0.5
Chloride; normal range 98-110 mmol/L						
Mean	103.5	102.9	-0.6	104.3	103.0	-1.3
SD	1.78	2.12	2.69	3.61	1.67	3.44
Median	104.0	103.0	-1.0	103.5	103.0	-1.0
Range	100, 106	99, 107	-6, 5	99, 113	100, 106	-10, 4
Total protein; normal range 6.2-8.3 g/dL						
Mean	7.53	7.61	0.07	7.56	7.48	-0.08
SD	0.639	0.616	0.655	0.497	0.490	0.353
Median	7.40	7.50	0.00	7.60	7.45	-0.10
Range	6.6, 8.9	6.6, 8.7	-0.8, 1.7	6.6, 8.2	6.6, 8.4	-0.8, 0.4
Albumin; normal range 3.6-5.1 g/dL						
Mean	4.37	4.30	-0.07	4.26	4.19	-0.07
SD	0.275	0.211	0.224	0.250	0.280	0.192
Median	4.40	4.30	-0.10	4.20	4.20	-0.10
Range	4.0, 5.1	3.7, 4.6	-0.5, 0.4	3.9, 4.9	3.8, 5.0	-0.3, 0.3
Alkaline phosphatase; normal range 40-115 U/L (males), 33-115 U/L (females 20-49 years), and 33-130 U/L (females ≥50 years)						
Mean	68.2	77.1	8.9	81.2	80.8	-0.4
SD	24.88	24.03	24.44	25.31	21.90	18.94
Median	68.0	76.0	6.0	80.0	74.5	-1.5
Range	10, 118	48, 136	-32, 68	54, 154	48, 127	-48, 43
Total cholesterol; normal range 125-200 mg/dL						
Mean	162.7	191.3	28.6	164.1	182.3	18.1
SD	32.76	42.74	35.25	32.28	39.81	21.90
Median	162.0	189.0	30.0	160.0	182.0	17.0
Range	99, 232	119, 260	-39, 124	125, 248	129, 307	-26, 59
Triglycerides; normal range <150 mg/dL						
Mean	103.3	130.4	27.2	90.0	126.8	36.8
SD	46.46	61.23	53.72	33.23	64.74	50.35
Median	105.0	121.0	15.0	82.5	112.0	25.5
Range	44, 229	43, 240	-108, 121	45, 160	50, 255	-31, 136

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO_2=bicarbonate; SD=standard deviation.

[a] Only subjects who had data at the 2 time points (baseline and post-test) are included (19/20 subjects receiving buprenorphine SL film and 16/18 subjects receiving buprenorphine/naloxone SL film).

[b] Change from Baseline.

Data derived from Module 5.3.5.3, Statistical Table 14.7.18.2.2.

Mean levels of ALT at post-test were elevated over those at baseline, with mean changes of 20.7 U/L with buprenorphine SL film and 18.4 U/L with buprenorphine/naloxone SL film. Mean levels of AST at post-test were elevated over those at baseline, with mean changes of 7.7 U/L with buprenorphine SL film and 7.1 U/L with buprenorphine/naloxone SL film. No other hepatic function tests, including alkaline phosphatase, total bilirubin and albumin, exhibited abnormal changes during the study.

Total cholesterol and triglycerides were also elevated compared to baseline in both study groups. Mean increase over baseline for cholesterol was 28.6 mg/dL for buprenorphine SL film and 18.1 mg/dL for buprenorphine/naloxone SL film. For triglycerides, mean increases were 27.2 mg/dL and 36.8 mg/dL, respectively.

Safety in special populations

The incidence of AEs in the integrated phase II population of opioid dependent subjects was analysed per subgroups (sex, race, age [<21, 21-35, 36-50, >50 years]). None of these analyses revealed clinically relevant difference between subgroups and are not presented here in detail.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

System Organ Class[b] Preferred Term	Number (%) of Subjects			
	SUBUTEX N=206	Buprenorphine SL film N=351	SUBOXONE N=313	Buprenorphine/ Naloxone SL film N=459
At least 1 adverse event leading to discontinuation[c]	**1 (0.5%)**	**5 (1.4%)**	**3 (1.0%)**	**9 (2.0%)**
Gastrointestinal Disorders	**1 (0.5%)**	**5 (1.4%)**	**3 (1.0%)**	**7 (1.5%)**
Vomiting	1 (0.5%)	5 (1.4%)	2 (0.6%)	7 (1.5%)
Nausea	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Gastritis	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Infections and Infestations	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.2%)**
Upper respiratory tract infection	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.2%)**
Skin and Subcutaneous Tissue Disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (0.2%)**
Drug eruption	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

[a] Includes Studies 20-A70-AU, 20-A71-AU, 20-A72-AU, 20-197-SA, 20-A78-AU, 20-250-SA, 20-272-SA, 20-273-SA, 20-277-SA, 20-276-SA, 20-B17-AU, 20-B20-AU, 20-A79-AU, 20-A90-AU, 20-290-SA, 20-291-SA, 20-293-SA, 20-B24-AU and 1003395.

[b] Adverse events were coded using MedDRA version 11.0 terminology.

[c] Every event is counted only once within subject, treatment group, SOC and PT. Because these are crossover studies that compared different treatments and routes of administration, the number of subjects exposed to each study drug formulation exceeds the total number of subjects in the studies. The table is organised by decreasing frequency of SOC, then by PT overall. Not all subjects who discontinued receiving study drug discontinued due to an AE.

Data derived from Module 5.3.5.3, Statistical Table 14.7.7.1.

Post marketing experience

Suboxone SL film has received marketing approval in the USA (30 August 2010), Australia (18 February 2011) and Malaysia (25 July 2013) and is currently marketed in these countries. The most recent data concerning the safety of Suboxone SL film can be found in the PBRER covering the period 31 July 2017 to 30 July 2018 (dated 01 October 2018).

The post-marketing experience data presented in Mod. 2.7.4 covers the period 30 August 2010 to 30 July 2018. All spontaneously reported adverse reactions from the markets where Suboxone SL film is marketed (USA, Australia, Malaysia) were included.

Though Suboxone tablets have been discontinued in the United States, Suboxone film had been available in the market for more than 2.5 years at the time of tablet discontinuation. Hence, safety data relating to the switch from tablets to films may only be obtained from this 2.5 year period of common parallel marketing of both formulations.

Oral reactions

During the PBRER reporting period 27 September 2010 to 26 September 2013, the occurrence of oral reactions was identified as a potential safety signal for Suboxone SL film by the Applicant on 20 September 2011. Following medical evaluation on 21 June 2013, the Preferred Terms of glossitis, stomatitis, and tongue disorder were confirmed as validated safety signals and terminology was added to the Reference Safety Information for Suboxone SL film. Oral reactions have been added as an important identified risk for Suboxone SL film.

Cases resulting in death

Cumulatively, there have been 635 events classified as fatal events in Suboxone SL film (reporting rate 15.8 events per 100,000 patient years) from 2010 until 30 July 2018.

Potential relationship with switching between SL tablets and films

The cases received cumulatively that mention both Suboxone tablet and film do not provide clear information regarding any temporal association of a fatal or otherwise serious event occurring at the time of or in response to switching from Suboxone tablet to film.

In relation to switching between Suboxone tablet and film and the occurrence of fatal or non-fatal overdose, 102 events of Overdose (79 events of Intentional overdose; 32 events of Prescribed overdose, i.e., prescribed at a higher dose than described in the approved label) were reported. Due to limited information in a majority of cases, the timing of overdose and intentional overdose is unclear if related to switching between products versus occurring at another time during treatment.

2.6.1. Discussion on clinical safety

The safety profile for the Suboxone SL tablets is well established. For the newly developed Suboxone SL film strips the same fixed combination 4:1 ratio of buprenorphine and naloxone is applied. Dose strengths are partly overlapping (2/0.5 mg and 8/2 mg SL films) and the proposed dose range (maximum daily dose of 24 mg) is the same in Europe. The 12/3 mg dose strength, subject of the MAA for the films, is not approved for the SL tablets. On the other side, the highest 16/4 mg dose strength is approved for the tablets, however, in not applied for as a film formulation.

The total number of subjects exposed to the Suboxone films during the clinical development is acceptable (N=459 healthy volunteers during PK studies, N=420 in phase II studies, N=1173 during the run-in-phase of the phase III studies for the buprenorphine depot injection RBP-6000 programme). In the context of the present line extension procedure the focus is on oral mucosa local tolerability of the new film dosage form. Local tolerability was routinely monitored throughout the PK trials in healthy volunteers and was systematically monitored in open-label study RB-US-07-0001.

The TEAE profile obtained in healthy volunteers corresponds to the AE profile typically expected after opioid administration with high incidence of gastrointestinal and nervous system disorders. Notably, in neither of the treatment groups administration site disorders (reflecting local tolerability) rank among TEAEs occurring in $\geq$ 2% of subjects.

It is noted that the portion of subjects experiencing at least 1 AE was considerably higher for SL films (N=301/459, 65.6%) as compared to SL tablets (N=150/313, 47.9%), which may be related to the higher buprenorphine exposure consistently observed after film administration. On the other side, it has to be taken into consideration that a portion of observed AEs (mainly GI) may be due to concomitant naltrexone administration.

As concerns AESIs, oromucosal placement of the film strips was locally well tolerated. Oral mucosal erythema was reported in only 2 of 194 SL patients [1%] resp. in 6 out of 188 [3.2%] of buccal patients after active monitoring pre- and post-administration. It is reminded that drug exposure in study RB-US-07-0001 was considerably high, expanding over a twelve week treatment period and involving daily administration of more than one treatment unit, given the mean daily dose of about 15 mg buprenorphine. A causal relationship between toothache (the second often oral cavity AE in the total population) and study drug administration is unlikely.

There were no deaths during the trials.

Mild elevations in hepatic transaminases were observed in study RB-US-07-0002. During phase II study RB-US-07-0002 opioid dependent subjects were stabilized on morphine and thereafter buprenorphine films or buprenorphine / naloxone films (blinded) were induced. Treatment with films went over 5 days. Abnormal hepatic function is listed in SmPC section 4.8. Both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate to severe hepatic impairment after single dose administration (SmPC section 4.4).

As regards the safety of switching between the tablet and film dosage form, it is to be taken into account that consistent bioequivalence between the film and tablet formulation could not be established. However, about similar buprenorphine levels were observed with a clear tendency for higher buprenorphine exposure after film administration (single dose studies 20-250-SA and 20-273-SA: Cmax increase by 21.6 to 27.8%, AUClast increase by 16.4 to 20.1%). The associated risks (risk of overdose if switching from tablets to films resp. risk of underdosing if switching in the inverse direction) are adequately addressed in SmPC section 4.2 Evaluation clinical trial data (phase II study RB-US-07-0001 in patients, previously receiving 4-32 mg buprenorphine SL tablets, being switched to sublingual / buccal films) and post-marketing data from the 2.5 year period of common marketing of the films and tablets do not point to undue safety risks associated with switching between the two formulations.

2.6.2. Conclusions on the clinical safety

The safety profile for the Suboxone SL tablets is well established. For the newly developed Suboxone SL film strips the same fixed combination 4:1 ratio of buprenorphine and naloxone is applied. Dose strengths are partly overlapping (2/0.5 mg and 8/2 mg SL films) and the proposed dose range (maximum daily dose of 24 mg) is the same in Europe. The 12/3 mg dose strength, subject of the MAA for the films, is not approved for the SL tablets. On the other side, the highest 16/4 mg dose strength is approved for the tablets, however, in not applied for as a film formulation.

The total number of subjects exposed to the Suboxone films during the clinical development is acceptable (N=459 healthy volunteers during PK studies, N=420 in phase II studies, N=1173 during the run-in-phase of the phase III studies for the buprenorphine depot injection RBP-6000 programme). In the context of the present line extension procedure the focus is on oral mucosa local tolerability of the new film dosage form. Local tolerability was routinely monitored throughout the PK trials in healthy volunteers and was systematically monitored in open-label study RB-US-07-0001.

The TEAE profile obtained in healthy volunteers corresponds to the AE profile typically expected after opioid administration with high incidence of gastrointestinal and nervous system disorders. Notably, in neither of the treatment groups administration site disorders (reflecting local tolerability) rank among TEAEs occurring in $\geq$ 2% of subjects.

It is noted that the portion of subjects experiencing at least 1 AE was considerably higher for SL films (N=301/459, 65.6%) as compared to SL tablets (N=150/313, 47.9%), which may be related to the higher buprenorphine exposure consistently observed after film administration. On the other side, it has to be taken into consideration that a portion of observed AEs (mainly GI) may be due to concomitant naltrexone administration.

As concerns AESIs, oromucosal placement of the film strips was locally well tolerated. Oral mucosal erythema was reported in only 2 of 194 SL patients [1%] resp. in 6 out of 188 [3.2%] of buccal patients after active monitoring pre- and post-administration. It is reminded that drug exposure in study RB-US-07-0001 was considerably high, expanding over a twelve week treatment period and involving daily administration of more than one treatment unit, given the mean daily dose of about 15 mg buprenorphine. A causal relationship between toothache (the second often oral cavity AE in the total population) and study drug administration is unlikely.

There were no deaths during the trials.

Mild elevations in hepatic transaminases were observed in study RB-US-07-0002. During phase II study RB-US-07-0002 opioid dependent subjects were stabilized on morphine and thereafter buprenorphine films or buprenorphine / naloxone films (blinded) were induced. Treatment with films went over 5 days. Abnormal hepatic function is listed in SmPC section 4.8. Both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate to severe hepatic impairment after single dose administration (SmPC section 4.4).

As regards the safety of switching between the tablet and film dosage form, it is to be taken into account that consistent bioequivalence between the film and tablet formulation could not be established. However, about similar buprenorphine levels were observed with a clear tendency for higher buprenorphine exposure after film administration (single dose studies 20-250-SA and 20-273-SA: Cmax increase by 21.6 to 27.8%, AUClast increase by 16.4 to 20.1%). The associated risks (risk of overdose if switching from tablets to films resp. risk of underdosing if switching in the inverse direction) are adequately addressed in SmPC section 4.2 Evaluation clinical trial data (phase II study RB-US-07-0001 in patients, previously receiving 4-32 mg buprenorphine SL tablets, being switched to sublingual / buccal films) and post-marketing data from the 2.5 year period of common marketing of the films and tablets do not point to undue safety risks associated with switching between the two formulations.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Important identified risks	• Abuse, misuse and diversion • Use in patients with hepatic impairment • Hepatic disorders • Drug withdrawal syndrome • Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child
Important potential risks	None
Missing information	None

Pharmacovigilance plan

All studies considered additional PhV activities for suboxone have been completed.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern Safety

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Abuse, misuse and diversion	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 6.5, and 6.6 PL section 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Special and restricted medical prescription Pack size: SUBOXONE sublingual tablets available in 7- or 28-tablet blister packs SUBOXONE sublingual films available in packs of 7, 14, 28 or 30 individual sachets	AE follow-up form for adverse reaction

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	
Use in patients with hepatic impairment	Routine risk minimisation measures: SmPC sections 4.2, 4.3 and 4.4 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Hepatic disorders	Routine risk minimisation measures: SmPC section 4.4 PL sections 2 and 4 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Drug withdrawal syndrome	Routine risk minimisation measures: SmPC sections 4.2 and 4.4 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction
Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures: None	AE follow-up form for adverse reaction

Conclusion

The CHMP and PRAC considered that the risk management plan version 14.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to suboxone. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Suboxone SL film has the same indication as the currently approved Suboxone SL tablet product, i.e., substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

Opioid dependence remains a major risk factor for ill health and death. It can result in a range of problems for the users and their family and friends, as well as for the wider community. These problems include health and social costs (to both the individual and the community), including the risk of overdose, spread of diseases and family breakdown; health costs; economic costs associated with morbidity, mortality and absenteeism related to illicit drug use; and the cost of law enforcement for drug-related crime. A key aim of opioid dependence treatment programs is to bring individuals into a comprehensive treatment environment where medical, social and psychological issues are addressed in addition to treating individuals' dependence on heroin or other opioids. Another key aim is to stop individuals from injecting drugs to aid in reducing the spread of HIV and hepatitis.

3.1.2. Available therapies and unmet medical need

The buprenorphine-containing products Suboxone and Subutex have made a valuable contribution to the treatment of opioid dependence. Buprenorphine reduces both the craving for opioids and the severity of the opioid withdrawal syndrome. However, due to its opioid properties buprenorphine has the potential to be

diverted for misuse by various routes, including by intravenous (IV) injection. Diversion for misuse by IV injection is one of the main identified risks of buprenorphine treatment for opioid dependence.

The addition of the potent antagonist at mu-opioid receptors naloxone to Suboxone formulations is to deter parenteral misuse as it is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine or methadone.

Suboxone SL film was developed as a pharmacotherapy for opioid dependence. The film formulation provides an alternative dosage form to Suboxone SL tablets. It was developed with the intention of producing similar efficacy and safety to Suboxone SL tablets, but with additional safety and compliance features. In particular, the formulation was created for the purpose of reducing the risk of diversion for illicit use, reducing unintended and potentially dangerous exposure in children, and improving compliance to treatment.

When placed in the sublingual cavity and exposed to contact with saliva, the film is expected to instantly adhere to the mucosa, which makes it difficult to remove for subsequent illicit use, an important consideration in supervised dosing environments.

3.1.3. Main clinical studies

The purpose of the present line extension MAA is to introduce Suboxone sublingual / buccal films (2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg) as an additional (alternative) dosage form to the approved Suboxone SL tablets. Accordingly, the clinical data package relies upon the PK comparison between the SL tablets and films after SD administration within the scope of five pivotal single dose BE studies:

20-250-SA	1 x 2/0.5 mg SL film vs SL tablets vs buccal film
20-272-SA	4/1 mg, administered as 2 x 2/0.5 mg SL film vs SL tablets vs buccal film
20-273-SA	1 x 8/2 mg SL film vs SL tablets vs buccal film
10003395	12/3 mg, administered as 1 x 8/2 plus 2 x 2/0.5 mg SL film vs SL tablets vs buccal film
20-B20-AU	1 x 12/3 mg SL film vs 1 x 12/3 mg buccal film vs 1 x 8/2 plus 2 x 2/0.5 mg SL tablet

These SD bioequivalence studies were complemented by two 5-arm dose proportionality studies to compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buprenorphine/naloxone film strips:

20-291-SA	after sublingual film administration
20-293-SA	after buccal film administration

On top of the PK studies presented above, two phase II studies were conducted in support of the Suboxone SL film strip MAA.

The objective of the open-label study RB-US-07-0001 was to assess the safety and tolerability in opioid dependent patients of buprenorphine and naloxone soluble film administered either sublingually or bucally daily for 12 weeks with particular emphasis on adverse events on the oral mucosa.

The purpose of the double-blind phase II study RB-US-07-0002 was to compare the presence, degree, time course and profile of opioid withdrawal symptoms associated with induction onto buprenorphine soluble films

and buprenorphine/naloxone soluble films in persons with active opioid dependence. The primary outcome measure was the severity of withdrawal symptoms measured using the Clinical Opioid Withdrawal Scale COWS.

Within the context of the present line extension procedure, the PK study programme is considered pivotal, whereas the two phase II studies are considered to contribute supportive data to the overall clinical development.

3.2. Favourable effects

PK Similarity between the SL tablet and film formulation

Across the five SD bioequivalence studies the newly developed film formulation (administered sublingually and buccally) was compared with the established Suboxone SL tablets over the 2/0.5 mg to 12/3 mg dose range. A variety of results (both complying and exceeding the 80-125% acceptance range for BE) was obtained for Cmax resp. AUC of the two buprenorphine and naloxone analytes. While for the lower dose strengths (2/0.5 mg to 8/2 mg) exposure in buprenorphine / nalxone was more similar between the film and tablet dosage form, the difference between the two formulations was most apparent for the highest 12/3 mg dose strength yielding point estimators of 143.49 [127.99 – 160.86 CIs] for sublingual and 151.73 [137.84 – 167.02 CIs] for buccal buprenorphine Cmax.

Overall, BE could not consistently be shown across all dose strengths. However, in the present line extension procedure, consistent compliance with the formal BE acceptance criteria (90% CIs within 80-125%) is not considered an indispensable prerequisite for approvability.

The proposed SmPC wording takes due account of approximately similar, however, not consistently bioequivalent blood levels between the SL tablet and SL / buccal film formulation. When switching patients from the established tablets to the newly developed film formulation, the subject should start using the same nominal dose. In case the patient is switched from tablets to films, the patient should be monitored for over-medication. In the reverse case, switching from films to tablets, the patients should be monitored for withdrawal or other signs of under-medication. The Applicant's approach is considered acceptable by the CHMP.

Dose linearity

The results of the sublingual dose proportionality study 20-291-SA demonstrated that the new film strip formulation displays linear, however, not fully dose proportional increases in plasma concentrations in doses between 2/0.5 and 16/4 mg buprenorphine/naloxone after sublingual administration. After buccal administration (study 20-293-SA), however, linearity could only be demonstrated for the 4/1 mg to 16/4 mg dose range, however, not covering the entire range of newly developed film formulations (2/0.5 mg to 16/4 mg).

Summarized data including across study comparisons (all SD BE plus dose proportionality studies) show that plasma exposures to buprenorphine and naloxone increased linearly with the dose following SL and buccal administration of Suboxone films in the range of 2 mg/0.5 mg to 16 mg/4 mg. Data also show good reproducibility of the results across studies in terms of Cmax and AUC for both naloxone and buprenorphine.

Safety and tolerability in opioid dependent patients

Study RB-US-07-0001 demonstrates that the majority of opioid dependent subjects maintained on SL tablets could be switched to the film formulation and that about two thirds of included subjects completed the entire 12-wk treatment period receiving either sublingual or buccal buprenorphine / naloxone films.

However, it is concluded that interpretability of efficacy data is greatly compromised by design-related shortcomings of study RB-US-07-0001, i.e. open-label, outpatient design without systematic ban / assessment of additional opioid consumption from non-study sources and insufficient demonstration of dose adequacy at baseline and during treatment.

Nonetheless, within the context of the present MAA, it is considered that study RB-US-07-0001 provides supportive reassurance for the safety and tolerability of the Suboxone films (sublingual and buccal) in patients with OUD.

In study RB-US-07-0002 the focus is upon the potential of the new SL films to provoke opioid withdrawal symptoms due to the naloxone component. No comparison is made between SL tablets and SL films, but between mono-entity buprenorphine films vs fixed-combination buprenorphine/naloxone films. The mono-entity buprenorphine films are not marketed.

The good and rapid efficacy of buprenorphine and / buprenorphine/naloxone is demonstrated by the fact that even with the first 4 mg dose baseline COWS scores (about 9-10) are about halved (COWS score about 4) within two hours post administration. With the second 4mg dose, given two hours after the first dose, a further halving of the withdrawal symptoms (COWS score about 2) is achieved within about further two hours in both treatment arms. The study met the primary objective by showing that there was a statistically significant reduction ($p<0.0001$) between the peak scores during the 23.5 hours period after treatment initiation and those at baseline for both groups.

However, within the context of the present line extension procedure, a comparison between the established SL tablets and the newly developed films would have been more meaningful than comparing mono-entity buprenorphine with the fixed combination of buprenorphine / naloxone. It is therefore concluded that study 02 did not directly answer the question whether buprenorphine / naloxone SL tablets and SL films demonstrate a similar likelihood of successful treatment induction in illicit drug users. However, it did provide some insight into the experience of patients transitioning from a full agonist (morphine) to the buprenorphine/naloxone combination film strip. Therefore, study RB-US-07-0002 is considered to bring supportive clinical data to the overall data package for the new film formulation.

3.3. Uncertainties and limitations about favourable effects

Switch between SL and buccal film administration

As concerns the potential switch between the two modes of administration of the film formulation, the amended SmPC specifies that no further monitoring is required based on similarity of exposure, however, a cross-reference to PK results presented in section 5.2 was added:

Switching between sublingual and buccal sites of administration

The systemic exposure of buprenorphine between buccal and sublingual administration of Suboxone film is approximately similar (see section 5.2). Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

The comparison between the SL and buccal administration of the film formulation does not yield consistently bioequivalent exposure of buprenorphine / naloxone across the five pivotal SD BE studies. However, in the three BE studies focussing on single unit administration of the film (20-250-SA: 1 x 2/0.5 mg, 20-273-SA: 1 x 8/2 mg, 20-B20-AU: 1 x 12/3 mg) bioequivalent exposure of buprenorphine could be demonstrated between the two methods of administration. In studies with combined administration of more than one film

unit at a time (20-272-SA: 2 x 2/0.5 mg, 1003395: 1 x 8/2 mg plus 2 x 2/0.5 mg) bioequivalence could not be demonstrated between sublingual and buccal administration of the films. Overall, however, given the mix of bioequivalent and non-equivalent results, the proposed SmPC wording pointing to approximately similar systemic buprenorphine exposure allowing the switch between the sublingual and buccal film administration is considered acceptable.

Completeness of the data package

The newly developed 4/1 mg film formulation strength was neither included in any of the five SD BE studies nor in one of the two dose proportionality studies. Provision of in vivo data on the 4/1 mg dose strength can be waived since the 2/0.5 mg and 4/1 mg film dose strengths are obtained from the same bulk, hence are dose weight multiples. Therefore, the BE study results obtained with the 2/0.5 mg formation can be extrapolated to the dose proportional 4/1 mg dose strength. Given the linear increase of Cmax and AUC with increasing doses (2/05 mg to 16/4 mg dose range), both across studies and within dose proportionality studies, it is therefore justified to waive generating in vivo PK data for the 4/1 mg dose strength.

Dose proportionality studies

Both dose proportionality studies are limited by the fact that the dose range examined (2/0.5 mg to 16/4 mg) do not cover the maximum daily dose (24/6 mg according to the SmPC) and that the 4/1 mg dose was administered as 2 x 2/0.5 mg film instead of the newly developed 4/1 mg film formulation.

In-vivo disintegration time

Suboxone is administered under supervision of personnel of the opioid dependence treatment unit - at least at treatment initiation. Even in these supervised dosing environments it has been reported that subjects may remove the sublingually placed tablet for subsequent illicit use. Any notable difference in disintegration time between the SL tablets and the films would be considered as a relevant advancement.

The benefit of the new film formulation in terms of acceleration of sublingual disintegration time (as compared to the SL tablets) appears small. During the BE studies, the SL film strips disintegrated on average about 1-3 minutes earlier as compared to the SL tablets (after about 5-8 min vs 7-11 min).

The small difference in disintegration time between the film and tablet formulation was confirmed in the literature study referenced by the Applicant. A group of Australian authors (Lintzeris et al 2013) compared buprenorphine/naloxone SL tablets and SL films and found a difference in dissolution time of only 1 minute (173 $\pm$ 71 vs 242 $\pm$ 141 seconds) in n=92 OUD patients.

Removability of administered films

In line with the small differences in disintegration time between tablets and films, removability of administered doses (even after supervised dosing) is likely to remain an issue in opioid substitution therapy with Suboxone.

The patients' ability of removing the films 30 sec resp. 1 minute post-administration in relation to the number of film units that were administered sublingually at a time (simultaneous placement of 1-4 films) was tested by Lintzeris and co-workers (literature provided by the Applicant). The authors found that the ability to wholly or partially remove the film was related to the number of films dosed, with more participants able to remove the film when more than two films were dosed at the same time. One minute post-administration no participant (n=36) was able to remove parts of the film if only one film unit was administered. Focussing on removability of the entire film as a whole, no participant was able to remove the entire film within 1 minute if up to two films were administered.

More recent literature reports by Larance et al.(2014, 2016) demonstrated that the portion of removal of doses after supervised dosing was about equal between the BNX tablets and BNX films based on surveys conducted in Australian patients being treated within the scope of opioid substitution therapy (N=543).

There are strategies to counteract removability of applied doses like e.g. safeguarding that patients moisten their mouth prior to dosing and not applying more than two films at once.

3.4. Unfavourable effects

Bioequivalence between the film and SL tablet formulation could not consistently be shown across all dose strengths. In particular for the highest 12/3 mg dose strength the difference between the two formulations was most apparent, yielding point estimators of 143.49 [127.99 – 160.86 CIs] for sublingual and 151.73 [137.84 – 167.02 CIs] for buccal buprenorphine Cmax.

In the proposed SmPC it is taken account of approximately similar, however, not consistently bioequivalent blood levels between the SL tablet and SL / buccal film formulation. When switching patients from the established tablets to the newly developed film formulation, the subject should start using the same nominal dose. Thereby the risk for over-medication occurs in case the patient is switched from tablets to films. Conversely, switching from films to tablets, the patients are at risk of withdrawal or other signs of under-medication. The SmPC recommends monitoring the patient when switching between dosage forms and adjust the dose, if appropriate,

The totality of data obtained from PK studies in healthy volunteers and phase II data obtained in opioid dependent subjects demonstrates that the safety profile of Suboxone SL film is consistent with the known safety profile of Suboxone SL tablets and does not point to unexpected safety signals for the newly developed sublingual and buccal film formulation. Therefore, apart from the above unfavourable effects regarding necessary dose adaptions when switching between dosage forms, there are no unfavourable effects of the newly developed film formulation to be expected.

3.5. Uncertainties and limitations about unfavourable effects

As regards the safety of switching between the tablet and film dosage form, it is to be taken into account that consistent bioequivalence between the film and tablet formulation could not be established. However, similar buprenorphine levels were observed with a clear tendency for higher buprenorphine exposure after film administration (single dose studies 20-250-SA and 20-273-SA: Cmax increase by 21.6 to 27.8%, AUClast increase by 16.4 to 20.1%). The associated risks (risk of overdose if switching from tablets to films resp. risk of underdosing if switching in the inverse direction) can hardly be evaluated based on post-marketing data. However, in the US, marketing of the SL tablets was terminated about 2.5 years after the newly developed films had been introduced. The obtained post-marketing data from the 2.5 year period of common marketing of the films and tablets do not point to undue safety risks associated with switching between the two formulations.

In relation to switching between Suboxone tablet and film and the occurrence of fatal or non-fatal overdose, 102 events of Overdose (79 events of Intentional overdose; 32 events of Prescribed overdose, i.e., prescribed at a higher dose than described in the approved label) were reported. Due to limited information in a majority of cases, the timing of overdose and intentional overdose is unclear if related to switching between products versus occurring at another time during treatment.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The present line extension procedure is intended to introduce Suboxone films for sublingual resp. buccal application as an additional dosage form to the already established Suboxone SL tablets. Accordingly, from the clinical perspective, the main focus is on demonstration of similar PK profiles between the two dosage forms.

Largely similar, although not consistently bioequivalent, PK profiles between the films and the SL tablets could be shown. Across the various strengths a consistently higher systemic exposure of buprenorphine, particularly after buccal administration, was observed. The associated risk of increased buprenorphine exposure is overmedication if patients are switched on 1:1 dose basis from SL tablets to the films. The risk of overmedication (when switched from SL tablets to the films) on the one side, and, in the reverse case, the risk for opioid withdrawal (when switched from films to SL tablets) on the other side, is addressed in section 4.2 of the proposed SmPC. It is recommended to switch patients starting from the same nominal dose and closely monitor the patient thereafter. If required, further dose adjustments are to be undertaken.

The risk of potential overmedication resp. withdrawal in case of switch is imminent as long as both the SL tablets and the films are marketed in parallel. In the US, where the films have been approved in 2010, marketing of the SL tablets has been terminated about 2.5 years thereafter.

The purported advantage of the newly developed films is an acceleration of in vivo disintegration after oromucosal placement as compared to the SL tablets. However, the overall difference in sublingual disintegration time appears small. The SL film strips disintegrated on average about 1-3 minutes earlier as compared to the SL tablets (after about 5-8 min vs 7-11 min) (based on in vivo disintegration data obtained during five BE studies).

The small difference in disintegration time between the film and tablet formulation was confirmed in the literature study referenced by the Applicant. A group of Australian authors (Lintzeris et al 2013) compared buprenorphine/naloxone SL tablets and SL films and found a difference in dissolution time of only 1 minute (173 $\pm$ 71 vs 242 $\pm$ 141 seconds) in n=92 OUD patients.

In line with the small differences in disintegration time between tablets and films, removability of administered doses (even after supervised dosing) is likely to remain an issue in opioid substitution therapy with Suboxone.

The patients' ability of removing the films wholly or partially was related to the number of films dosed, with more participants being able to remove the film when more than two films were dosed at the same time.

3.6.2. Balance of benefits and risks

The clinical data package that was provided in support of the newly developed Suboxone film formulation comprising PK data and data from phase II studies is considered comprehensive and adequate. The totality of clinical data did not point to a particular safety risk for the films, e.g. in terms of local tolerability. However, in terms of accelerated oromucosal disintegration time the advantage of the films over the SL tablets (if any) is only very modest (only 1 minute [173 $\pm$ 71 vs 242 $\pm$ 141 seconds] in n=92 OUD patients, Lintzeris et al. 2013).

In line with about similar disintegration time, the ability to remove administered films appears to be similar between the two dosage forms (Larance et al. 214, 2016). There are two factors suitable to counteract removability of films after supervised dosing: subjects should moisten their mouth prior to dosing (in order to facilitate early adhesion) and the number of simultaneously applied films should be limited to two film units. These measures, emerging from literature reports, are to be adequately reflected in the product particulars. The product information of the films should not contain any promotional claim for improvement over the SL tablets in terms of accelerated disintegration resp. removability of administered doses.

3.6.3. Additional considerations on the benefit-risk balance

n/a

3.7. Conclusions

The overall B/R of Suboxone sublingual films is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Suboxone 2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films is favourable in the following indication:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Suboxone is indicated in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Suboxone Sublingual film subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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.