18 December 2014
EMA/805547/2015
Committee for Medicinal Products for Human Use (CHMP)

Mysimba

(naltrexone/bupropion)

Procedure No. EMEA/H/C/003687

Applicant: Orexigen Therapeutics Ireland Limited

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

AELDSM	Adverse events leading to discontinuation of study medication
BOCF	Baseline Observation Carried Forward
DDI	Drug-drug interaction
DKMA	Danish Health and Medicines Authority
EC_{90}	90% effective concentration
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FCI	Food Craving Inventory
FDA	Food and Drug Administration
FDC	Fixed-dose combination
fMRI	Functional magnetic resonance imaging
GCP	Good Clinical Practice
GI	Gastrointestinal
GLPs	Good Laboratory Practices
hr	Hour
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPLC	High performance liquid chromatography
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IDS-SR	Inventory of Depressive Symptomatology- Self Reported
IR	Immediate release
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IWQOL	Impact of Weight on Quality of Life
kg	Kilogram
LDL	Low-density lipoprotein
LC/MS/MS	Tandem mass spectrometry
LHH	Likelihood to be helped or harmed
LOCF	Last Observation Carried Forward
LS	Least squares
LVF	Left ventricular function
m^2	Squared meter
MACE	Major Adverse Cardiovascular Events
MC4-R	Hypothalamic melanocortin 4 receptors
MEB	The Dutch Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
MHRA	The Medicines and Healthcare Products Regulatory Agency, UK
MI	Myocardial infarction
mL	Milliliter
MNAR	Missingness not at random
MOP-R	Mu-opioid receptor
MPA	Medical Product Agency, Sweden
MRP	Mutual Recognition Procedure
MSH	Alpha-melanocyte stimulating hormone
N	Number of subjects
N/A	Not applicable
NCA	Noncompartmental analysis
NB	Naltrexone hydrochloride /Bupropion hydrochloride combination
NB16	Naltrexone PR 16 mg/Bupropion PR 360 mg
NB32	Naltrexone PR 32 mg/Bupropion PR 360 mg
NB48	Naltrexone PR 48 mg/Bupropion PR 360 mg
ng	Nanogram
NICE	The National Institute for Health and Care Excellence
NNH	Number needed to harm
NNT	Number needed to treat
NOS	Not otherwise specified
OCT2	Organic Cation Transporter-2
PAWC	Pharmacologically weighted composite
PBO	Placebo
PCS	Potentially clinically significant
PD	Pharmacodynamics
PDCO	The Paediatric Committee at the European Medicines Agency
PET	Positron emission tomography
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PMRS	Pharmaceutical Manufacturing and Research Services
POMC	Hypothalamic pro-opiomelanocortin
PR	Prolonged release
QRS	QRS complex of ECG
QT	QT interval of ECG
QTc	Corrected QT interval
RMP	Risk Management Plan
SAEs	Serious adverse events
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standardised MedDRA Queries

SmPC	Summary of Product Characteristics
SOC	System organ class
SOPs	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitor
SPA	Special Protocol Assessment
SR	Sustained release
TEAEs	Treatment-emergent adverse events
THIN	The Health Improvement Network
Tmax	Time to maximum plasma concentration
TME	Targeted medical event
US	United States
Vc/F	Apparent volume of distribution of the central compartment
VTA	Ventral tegmental area
WHO	World Health Organisation
XENDOS trial	Xenical in the Prevention of Diabetes in Obese Subjects
XR	Extended release

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Orexigen Therapeutics Ireland Limited submitted on 2 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Mysimba, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 January 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

Naltrexone / Bupropion Orexigen is indicated in adults for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification.

Naltrexone / Bupropion Orexigen is indicated for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g. type 2 diabetes, dyslipidaemia, or hypertension).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a fixed combination medicinal product.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0188/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0188/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant did not seek scientific advice/Protocol Assistance at the CHMP.

Licensing status

The product has been given a Marketing Authorisation in the United States (US) on 10 September 2014.

1.2. Manufacturers

Manufacturer responsible for batch release

Central Pharma Contract Packaging Ltd.
Caxton Road, Bedford, Bedfordshire,
MK41 0XZ
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Heisterberg

Co-Rapporteur: Robert James Hemmings

CHMP Peer reviewer(s): Milena Stain

- The application was received by the EMA on 2 October 2013.
- The procedure started on 23 October 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 February 2014.
- During the meeting on 20 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 February 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2014.
- During the CHMP meeting on 24 July 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 September 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 October 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 October 2014.
- During the CHMP meeting on 23 October 2014, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on

17 November 2014.

- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 26 November 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 4 December 2014.
- The Rapporteurs circulated the updated Joint Assessment Report to all CHMP members on 12 December 2014.
- During the meeting on 18 December 2014 , 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 Mysimba.

2. Scientific discussion

2.1. Introduction

Obesity is defined as a state of excess body fat that frequently results in impairment of health. According to the WHO it may be expressed in adults in terms of the Body Mass Index (BMI = bodyweight (kilograms) / (height [metres²]) with BMI of between 18.5 and 24.9 representing the normal range, a BMI of 25 to 29.9 representing overweight and a BMI of ≥ 30 considered to represent obesity. Severe obesity is defined as BMI of ≥ 40 and is associated with a substantially greater health risk than a BMI of 30. In Asian and Pacific populations the limits are, however, defined lower.

BMI appears to rise gradually during most of adult life, peaks at around 60 years, and then declines. After age 65, the rate of weight loss occurs at an average rate of 0 to 0.65 kg/year, although there is substantial individual variation. Loss of muscle mass begins from 30 to 40 years of age and continues into old age, while body fat increases through most of adulthood. Compared to younger individuals with the same BMI, older subjects tend to have a greater proportion of fat and an increased proportion of visceral and abdominal fat. An increase in intra-abdominal fat is associated with greater mortality in both younger and older adults, even when it is independent of overall adiposity. However, the effect of BMI on mortality seems to differ quantitatively between older and younger subjects and obesity may have less of an effect on mortality in older individuals than in younger individuals. In childhood, BMI is age and gender specific.

Obesity is recognised as a chronic clinical condition that usually requires long-term therapy to induce and maintain weight loss and is considered to be the result of complex interaction of genetic, metabolic, environmental and behavioural factors, which are associated with increases in both morbidity and mortality.

Although the relationship is not linear, health risks increase with severity of obesity and include hypertension, atherogenic dyslipidaemia insulin resistance and type 2 diabetes mellitus, and cardiovascular disease (angina pectoris, claudication, venous thromboses and their major consequences such as pulmonary embolism). Obesity is associated with an increased risk of cardiovascular disease in adults and with less favourable cardiovascular risk factor status in children and adolescents. Obesity is also associated with an effect on cardiovascular morbidity and mortality, through association with hypertension, diabetes and dyslipidaemia.

The sleep apnoea syndrome, strongly associated with obesity, has an increased mortality. There is also an increased mortality from endometrial carcinoma in women and colorectal carcinoma in men. Hypertriglyceridaemia, reduced levels of high-density cholesterol, elevations of total and low-density cholesterol and abnormalities in haemostasis are also associated. Mechanical complications can severely impair quality of life. Obese patients have a significantly impaired quality of life, as objectively measured by several independent tests. Overweight and obesity after young adulthood has also been associated with future risk of dementia. The most likely explanation for this is accelerated vascular dementia in heavier adults.

The location of body fat is also a predictor of the relative health hazards of obesity. Several epidemiological studies have shown that the regional distribution of body fat is a significant and independent risk factor for cardiovascular disease. Subjects with visceral (android/ abdominal) obesity with excess fat in the upper (central) body region, particularly the abdomen, represent a subgroup of obese individuals with the highest risk for cardiovascular disease and are also at greater risk of metabolic complications when compared to patients with lower body (gynoid) obesity with increased fat in the lower body segment, particularly the hips and thighs. Recently, waist

circumference alone (measured at mid distance between the bottom of the rib cage and the iliac crest) has been found to be an integrated measure of obesity that is positively correlated with abdominal fat content and is an independent predictor of risk. There is a suggestion that change in waist circumference measurement has been shown to be a better correlate of change in visceral adipose tissue than change in waist hip ratio. There is no widely accepted clinical measure of central obesity in children. The technique of dual-energy x-ray absorptiometry (DEXA) has been shown to provide a direct, accurate, and precise measure of lean body mass and total fat mass, which allows quantification of fat mass in anatomically-defined regions of interest, and more precise evaluation of the impact of fat distribution. Other methods include computer tomography and magnetic resonance imaging.

The general goals of weight loss and management are to reduce body weight and to maintain a lower body weight over the long term.

Non-pharmacological options for treatment include nutritional education and modification (usually calorie restriction), behaviour modification, and increased activity and exercise. In severe obesity, very low calorie diets (VLCD) may be applied for a limited period of time and, finally, surgery as a last resort.

Pharmacological options are not usually recommended until at least a trial of an appropriate educing diet has proved insufficient, i.e. inadequate initial weight loss was achieved or the individual, despite continuing dietary advice, could not maintain an initial weight loss. Pharmacological options are only considered as an adjunct to dietary measures and physical exercise.

Currently the only centrally approved pharmacological option in EU is Xenical (orlistat) and Alli (orlistat). Orlistat inhibits the absorption of nutrients. Xenical (orlistat) has been centrally approved in July 1998 and Alli (orlistat) in July 2007. Alli is currently available as an OTC product.

Because current pharmacotherapies are extremely limited, an unmet clinical need for safe, effective, and well-tolerated medications persists; therefore, a new pharmacologic strategy with a good safety profile that results in significant weight loss would be beneficial.

Orexigen Therapeutics Inc. has developed a fixed-dose combination (FDC) product for the treatment of obesity composed of two currently marketed drug substances: bupropion hydrochloride (hereafter bupropion), a norepinephrine and dopamine reuptake inhibitor, together with naltrexone hydrochloride (hereafter naltrexone), a mu-opioid receptor antagonist.
In the EU, naltrexone and bupropion have been individually used for over 25 and 14 years, respectively, for chronic indications at doses comparable to (bupropion) or greater than (naltrexone) those recommended for naltrexone hydrochloride /bupropion hydrochloride combination (NB) FDC for the treatment of obesity.
Prolonged release formulations of bupropion are approved in the EU for the treatment of major depression and nicotine dependence. In 1999, bupropion (Zyban®) was first approved through the Mutual Recognition Procedure (MRP) as an aid in smoking cessation. In 2007, Bupropion (Wellbutrin® XR) also underwent the MRP procedure and was approved for the treatment of major depressive episodes. Bupropion is registered in all EU countries with the exception of Bulgaria.
Immediate release formulations of naltrexone are approved in EU for the treatment of opiate and alcohol dependence. Either the originator Nalorex® or several generic products are available in most of the EU Member States.

The rationale for the development of this combination product is that administration of naltrexone with bupropion would result in greater weight loss than either treatment alone. Both compounds affect key circuitry in two areas of the brain. The first is the arcuate nucleus of the hypothalamus, an area of the brain that plays a critical role in the control of food intake and energy expenditure. The

second is the mesolimbic dopaminergic reward system, a region of the brain that is important for processing the rewarding aspects of food and food related stimuli. Furthermore, both bupropion and naltrexone act in the mesolimbic reward system to influence eating behaviour. Pairing the long-established mu-opioid receptor antagonist naltrexone with bupropion was hypothesised to yield a more potent sustained effect on body weight than either agent alone.
The drug product proposed for marketing is available in one strength 8mg/90mg of naltrexone hydrochloride/bupropion hydrochloride as a prolonged release tablet for oral administration.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged-release tablets containing in a fixed dose combination of 8 mg of naltrexone and 90 mg of bupropion, as active substances per tablet.

Other ingredients are: cysteine hydrochloride, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, lactose anhydrous, lactose monohydrate, crospovidone, dye fd&c blue #2 aluminum lake, hypromellose, edetate disodium, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, macrogol and talc as described in section 6.1 of the SmPC.

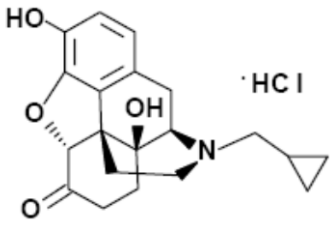
The product is available in PVC and PCTFE laminated blisters and sealed with an aluminium foil (PVC/PCTFE/PVC/Alu) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Naltrexone

Naltrexone hydrochloride is described in the Ph. Eur. The chemical name of the active substance is (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride, corresponding to the molecular formula $C_{20}H_{24}ClNO_4$ and has a relative molecular mass 377.85. It has the following structure:



The structure of the active substance has been confirmed by mass spectrometry, infrared, ^{1}H- and ^{13}C-NMR spectroscopy and X-ray crystallography, all of which support the chemical structure.

It appears as a white to slightly off-white, hygroscopic crystalline powder. It is freely soluble in water and slightly soluble in ethanol. The dissociation constant of naltrexone was determined to be pKa1 = 8.38 and pKa2= 9.93, and its partition coefficient (n-octanol/water) $logK_{ow}$ was determined to be 0.534.

The structure of naltrexone HCl has four stereogenic centers that are predetermined in the starting material.

There are possibly seven identified polymorphic forms. The relevant to the synthesis three polymorphic forms of naltrexone hydrochloride together with their corresponding XRPD spectra and DSC scans have been presented. The anhydrous form of naltrexone hydrocloride is routinely and consistently obtained from the synthesis used by the proposed manufacturer.

The active substance is packaged in material which complies with the relevant EC Regulation and Ph. Eur. requirements.

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

Manufacture, characterisation and process controls

Naltrexone hydrochloride is manufactured by a five step process from well-defined and adequately controlled starting materials. Reprocessing if needed is foreseen and described. The synthesis does not alter the configuration of the stereogenic centres established in the starting materials. Isolated intermediates have been identified and are controlled by appropriate specifications. The process has been described in sufficient detail and critical process parameters (CPPs) and in-process controls (IPCs) have been reported and are considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Sufficient information on potential and actual impurities (including potential genotoxic), their fate and control has been presented.

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

Specification

Naltrexone hydrochloride is controlled as per the current Ph. Eur. monograph. In addition to the tests listed in the Ph. Eur. monograph, the active substance specification includes controls of a potential genotoxic impurity and a residual solvent both specific to the applied synthetic process. The overall control strategy for impurities and catalysts is considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data for three commercial scale batches of the active substance were provided from the supplier and the product manufacturer. The results were similar between the proposed supplier and with the results obtained by the product manufacturer; they complied with the proposed specification and were consistent from batch to batch.

Stability

Stability data on 14 commercial scale batches stored for up to 60 months under long term conditions at 25 °C/ 60 % RH and for up to six months under accelerated conditions at 40 °C/ 75 % RH according to the ICH guidelines were provided. Stability batches were packaged in containers either identical or equivalent to the commercial one.

The investigated parameters were appearance, impurities, completeness of solution, water content, residual solvents and assay. The analytical methods were shown to be stability indicating.

No particular trend was observed, all the results were in line with the proposed specification. It was observed that for the batches manufactured initially, the content in residual solvents was higher, although within the acceptance limits. The batches manufactured recently had a lower content in

residual solvents. The results one impurity were out of specification at the 48 and 60 months interval while at the 36 month time point there was an increase in two other impurities. These observations,\ however, were made on a single batch of the older stability batches. Based on the provided information it was considered these were not related to any changes in manufacturing method or analytical method, but to handling of the samples in the older stability studies. None of these was observed for more recent stability batches and therefore it is not seen as a plausible concern.

Photostability study was performed in accordance with ICH guideline; the results did not show any significant changes compared to the control.

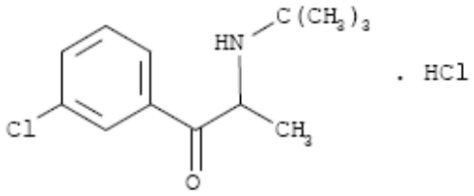
Stress studies have been performed at high heat, boiling hydrochloric acid, boiling sodium hydroxide and boiling phosphoric acid and UV light. Degradation did not occur under UV light but naltrexone has been found to degrade in the other tested stressed conditions.

Based on presented stability data, the proposed re-test period and storage conditions for naltrexone are acceptable.

General information

Bupropion

The chemical name of the active substance is ((±)-2-(tert-butylamino)-3'-chloropropiophenone hydrochloride, corresponding to the molecular formula C13H18ClNO.HCl and a relative molecular mass of 276.21. It has the following structure:



The structure of the active substance has been confirmed by elemental analysis, mass spectroscopy, 1^{H}-NMR , IR- and UV-spectroscopy along with the chemical pathway used for the synthesis.

It appears as a white to almost white, hygroscopic crystalline powder. It is freely soluble in methanol, soluble in water and ethanol, very slightly soluble in acetone. The pH of a 5 % aqueous solution of bupropion hydrochloride is about 5.0.

Bupropion HCl has one asymmetric carbon atom. It is produced as a racemate with no optical activity since the relevant synthesis reaction is not stereospecific. Cis-trans and threo-erythro isomerisations do not occur.

Five polymorphic forms of bupropion hydrochloride are known. XRPD and DSC studies confirmed the presence of only one crystalline form, the same from both manufacturers.

The active substance is packaged in material which complies with the relevant EC Regulation and Ph. Eur. requirements.

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

Manufacture, characterisation and process controls

Two manufacturers are proposed for the manufacture of the active substance, both following the same synthetic route. The manufacture consists of two chemical reaction steps, purification and milling. The proposed starting materials are well-defined and, considering the overall control strategy

over the synthetic process, are considered acceptable. The synthesis has been described in sufficient detail and critical process parameters (CPPs) and in-process controls (IPCs) have been reported and are considered satisfactory.

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 (including genotoxic) and degradation products have been characterised and are adequately controlled.

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

Specification

The active substance specification includes appropriate tests and limits for: appearance (visual), identity (bupropion: IR, HPLC, chloride: chemical reaction), water content (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC) and particle size (laser light diffraction). The same specification applies to the material from both suppliers.

The analytical methods used have been adequately described and validated as appropriate in accordance with the ICH guideline.
Batch analysis data for 14 full scale batches from both suppliers (8+6) were provided.

Additional data for 15 batches manufactured at a different site used in the clinical programme were also submitted. All results were within the specifications and consistent from batch to batch. The quality of the material from both suppliers is considered comparable.

Stability

Stability data on 20 commercial scale batches of active substance from the first supplier stored for up to 72 months under long term conditions at 25 °C/ 60 % RH and for up to six months under accelerated conditions at 40 °C/ 75 % RH according to the ICH guidelines were provided. The packaging used for the for the stability studies simulates the packaging used for the commercial product. The investigated parameters were: description, related substances, water and assay. Forced degradation studies showed the analytical methods to be stability indicating. All the results were in line with the proposed specification.
No formal photostability study has been performed though samples were exposed light in the stress testing study. The samples showed no significant difference with respect to unexposed samples.

Stability data on three commercial scale batches of active substance from the other supplier stored for up to 36 months under long term conditions at 25 °C/ 60 % RH and for up to six months under accelerated conditions at 40 °C/ 75 % RH according to the ICH guidelines were provided. The packaging used for the for the stability studies simulates the packaging used for the commercial product.
The active substance was tested in line with the shelf life specification by methods shown to be stability indicating. All the results were in compliance with the acceptance criteria in the proposed specification. No particular trend was observed.
Photostability study was conducted according to ICH guideline Q1B requirements. Bupropion hydrochloride showed only a very slight degradation.

Forced degradation studies were performed by both suppliers under acidic, basic, oxidative, thermic and light treatment. No degradation was observed under acid, thermic and light exposure. Various degree of degradation was observed for samples in different conditions.

Based on presented stability data, the proposed re-test period and storage conditions are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Mysimba fixed dose combination tablets are comprised of a trilayer core that is composed of two active layers containing one active substance each and an inert layer separating the active layers. The two active layers were developed separately.
Various formulations of bupropion hydrochloride were developed utilising different type of solid forms and different manufacturing methods. The final formulation and manufacturing method were selected on the criterion of showing the desired dissolution profile. L-cysteine hydrochloride is used as a stabiliser for bupropion hydrochloride which has been shown susceptible to hydrolysis. A detailed overview of the different compositions of the bupropion layer was provided.
The development of the formulation and manufacturing method of naltrexone layer has also been described in sufficient detail. EDTA is used as a stabiliser in the active naltrexone layer. Due to the low content of low content of naltrexone in the formulation, blend and content uniformity were evaluated in detail, and the manufacturing process was optimised in this respect. .
The trilayer tablet was formulated from the combination of the two individual active layers and an inert layer between these two layers.
The middle inert layer disintegrates rapidly in order to separate the two active layers, which then release each active substance independently from each other. The blue dye in the inert layer is used as a processing aid to differentiate layers during compression.
All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Non-compendial excipients are controlled by suitable in-house monographs. There are no novel excipients used in the finished product formulation. The role and need for the two stabilisers cysteine HCl and EDTA were explained and the amounts of stabilisers used in the individual layers were justified supported by data. The full list of excipients is included in section 6.1 of the SmPC.
Both active substances are soluble in water and the suppliers consistently manufacture and sufficiently control the same polymorph. In the clinical development a different polymorph of naltrexone hydrochloride was used than the one proposed. However taking into account the aqueous solubility of naltrexone, polymorphism is not expected to be a significant factor with respect to bioavailability. It was further demonstrated that other bupropion potential crystalline forms that might be generated during product manufacture are also very soluble, and the properties of the tablets were not affected. Therefore polymorphism is not deemed critical with regard to the product quality. Additionally, it has been shown by stability studies that both substances remain in the same crystalline form during storage. Also the proposed particle size specification is deemed sufficient taking also into account the aqueous solubility of both active substances.
The proposed dissolution method is an important quality control tool for the performance of this specialised pharmaceutical form. The bioavailability batch showed acceptable pharmacokinetic exposure.
It is considered that the variability observed *in vitro* is not clinically relevant from a pharmacokinetic and safety perspective. Based on the presented information the proposed dissolution method is considered sufficiently discriminatory. The dissolution specification was based on clinical data and on the *in vitro* performance of the clinical batches and the bioavailability batch.
Dissolution studies of one batch of the trilayer tablet in media containing varying concentrations of ethanol to test potential dose dumping of bupropion and naltrexone as per the QWP Q&A was performed. It was demonstrated that the dissolution of both drug substances was reduced by ethanol i.e. the trilayer tablets do not exhibit dose dumping of bupropion or naltrexone in the presence of alcoholic dissolution media. Despite the slower release in the presence of ethanol, the full dose ultimately is available once the tablet fully dissolves, albeit later than in the absence of alcohol. Additional clinical justification was provided and a wording in the SmPC has been proposed to take a

conservative approach to a potential interaction between the Mysimba and alcohol. This is further assessed in the clinical assessment report.
The manufacturing process development activities were primarily focused around the achieved introduction of the middle fast disintegrating inert layer.
The processes related to the bupropion hydrochloride and naltrexone hydrochloride parts of the dosage form were independently developed and then combined with the process for the inert middle layer to provide the final overall process. The development of the early clinical batches was also described. The majority of Phase III clinical batches and all of the registration batches were manufactured by the proposed process at the proposed commercial site.

Mysimba tablets are packaged in PVC/PCTFE/Aluminium blisters, a material which complies with the Ph. Eur. requirements. The choice of the container closure system has been supported by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Manufacturing Mysimba film-coated tablets, consists of the following steps: wet granulation of the bupropion layer, blending of the components of the middle (inert) layer, blending of the naltrexone layer , compression of the three solid mixtures to the trilayer tablet core, film-coating and packaging.
The manufacturing process of the finished product is considered a non-standard process due to the prolonged release properties of the two separate layers and the low content of naltrexone in the final tablet.
Process intermediates are defined and controlled by appropriate specifications; holding times have been qualified for these intermediates. The critical process parameters and in-process controls have been presented and are justified in relation to how the quality attributes are affected.
Process validation data of three production scale batches were provided. All results comply with the specifications.

Overall it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product Mysimba film coated prolonged release tablets of consistent quality, complying with the designated specification.

Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), identification of bupropion HCl (HPLC, HPLC-DAD or HPLC-PDA), identification of naltrexone HCl (HPLC, HPLC-DAD or HPLC-PDA), assay of bupropion HCl and naltrexone HCl (HPLC), naltrexone and bupropion related substances (HPLC), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution of bupropion HCl and naltrexone HCl (Ph. Eur.- HPLC) and microbial limits (Ph. Eur.). Impurities were qualified by toxicological and clinical studies and appropriate specifications have been set according to ICH Q3A. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch results were provided for 52 batches used as clinical batches, three stability and three registration batches. The registration batches and many of the other batches were manufactured using active substances from the proposed manufacturers. Some of the batches were manufactured at different sites and / or from material from other manufacturers used only during development. The batch size of the presented batches varies and includes at least two full scale batches. The presented data confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three pilot scale stability batches of finished product stored in the intended commercial package for 36 months under long term conditions at 25 °C / 60 % RH, intermediate conditions at 30 °C / 65 % RH and for six months under accelerated conditions at 40 °C / 75 % RH according to ICH guidelines were provided.
In addition, supportive stability data were provided for three lower strength batches of naltrexone / bupropion 4 mg / 90 mg using bupropion from the second supplier and naltrexone from an alternative manufacturer (used for development only).

Samples were tested for the parameters as per the release specification with the exception of content uniformity. The analytical procedures used are stability indicating.

All results were within the proposed specification with the exception of some out-of-specification results of the related substances of both naltrexone and bupropion observed after 6 months in accelerated conditions and after 36 months in the intermediate conditions. However, under normal long term conditions all results were within the specification.
The results and their statistical analysis demonstrated that tablets manufactured with active substances from different sources are comparable.

In addition, one batch was tested in a photostability study performed in accordance with the ICH guidance. The results were well within the specification limits, and it was concluded that the product is not sensitive to light.

Tablets were subjected also to forced degradation studies under heat and UV light, whereas aqueous solutions of naltrexone HCl and bupropion HCl were subjected to alkalic, acidic and oxidative conditions demonstrating the methods are stability indicating.

Overall based on the presented information the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agent
It is confirmed that the lactose used in the manufacture of Mysimba is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

L-Cysteine Hydrochloride used in the product manufacture is derived from acid hydrolysis of keratin sourced from poultry feathers. The manufacturing process conditions used to manufacture L-cysteine from poultry feathers ensure that the material is unlikely to pose any TSE risk and presents a very low risk of infectious agent transmission such as those associated with viruses, bacteria or prions. A TSE/BSE statement from the supplier was provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The documentation on the active substances has been presented as ASMF from each of the suppliers. Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The product is formulated as a fixed-dose combination trilayer tablet for prolonged release oral delivery. The three layer formulation is justified. The excipients and the formulation of the trilayer tablet are justified. The finished product and its performance are controlled by appropriate specifications.

Mysimba is a specialised pharmaceutical dosage form due to the prolonged release properties of the two separate layers and the low amount of naltrexone hydrochloride manufactured by a non-standard manufacturing process which has been properly validated. The product is controlled by appropriate specifications. 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant submitted mainly literature data supporting the non-clinical aspects mostly related to each mono component. Three additional new non-clinical studies were conducted to support the NB application. *In vivo* animal and *in vitro* cellular models from literature sources were used to review the pharmacology and further define the mechanism of action for Naltrexone and Bupropion, with an emphasis on effects related to their established mechanisms in opioid/alcohol addiction (Naltrexone), depression (Bupropion), nicotine dependence (Bupropion), and the hypothesized mechanism of action of NB in the facilitation of weight loss.
For the fixed dose combination, NB, the Applicant has submitted one safety pharmacology study (Study No.l 1560-001) and two pharmacokinetics studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies and Secondary pharmacodynamic studies
No new pharmacodynamic (PD) studies with Naltrexone or Bupropion have been conducted by the Applicant to support the combined NB application. The Applicant refers to published literature on pharmacodynamic effects of both compounds and also to the pharmacodynamics stated for Naltrexone and Bupropion in the SmPCs for each mono component as additional supportive information. Generally, the PD data from the literature of Naltrexone and Bupropion is correctly cited by the Applicant. The amount of literature is quite comprehensive, in support of the current application.

Naltrexone

The mechanism of action of Naltrexone hydrochloride is not completely elucidated. However, the primary pharmacology of Naltrexone is believed to be occupation and competitive blockade of opioid receptors, in particular the mu opioid receptor.

Marks-Kaufmann et al (1984) showed a significant decrease in total calorie intake, following SC infusion of Naltrexone at 200 µg/kg/hr, administered by a surgically implanted mini-osmotic pump. However, the observed effect was only evident the first week after implantation, and no statistically significant reduced caloric intake, compared with saline, was evident in the second week. As the observed significant reduction in food intake was only present in Naltrexone-treated rats in the week following operation, and as both saline- and Naltrexone treated animals apparently reduce food intake in this time period, the influence of operation stress from implantation of osmotic mini pumps should be taken into account with relation to the apparent anorectic effect of Naltrexone in this study.

Extended-release of Naltrexone (50 mg/kg IM) decreased the food intake and body weight gain induced by olanzapine (Kurbanov et al. (2012). The authors did not see any effects on food intake or body weight gain when administering Naltrexone alone.

Naltrexone doses of 1-3 mg/kg administered SC to rats significantly decreased food seeking and binge-like eating in a study by Giuliano et al. (2012).

In mildly food restricted rats, Naltrexone significantly and dose-dependently suppressed short-term food intake (1, 4 and 20 hours post dosing) at doses of 0.32, 1 and 3.2 mg/kg IP (Liang et al., 2013). Additive effects on food intake reduction as well as food aversion learning was found for Naltrexone in combination with the glucagon-like peptide 1 (GLP-1) agonist, exendin-4.

Secondary pharmacodynamic effects of Naltrexone are generally believed to be mediated via mu opioid receptors and include increased gut motility, increase in luteinising hormone, a decrease in prolactin and blocking opioid-agonist-induced discriminative stimuli. Low dose Naltrexone has shown potential beneficial effects in a murine experimental autoimmune encephalomyelitis model as well as repression of tumour progression in mice transplanted with human epithelial ovarian cancer cells.

Bupropion

Bupropion was confirmed to be anorexic 2 to 4 hours after IP administration to rats at 12.5-75 mg/kg Bupropion (Zarrindast and Hosseini-Nia, 1988). However, in mice treated with Bupropion (20 and 40 mg/kg IP daily for 7 days), the effect was only evident at 1 hour post treatment and not 4 hours after treatment. In this latter study, no effects were observed on body weight (Billes and Cowley 2007). In a subsequent publication, a significant increase in food intake was observed in Bupropion treated animals (doses) on day 5 and the cumulative food intake was increased by 17% on Day 7.

The Applicant has stated in the Non-Clinical Overview, that '*Billes and Cowley (2008) administered acute intraperitoneal (IP) injections of Bupropion, GBR12783 (a selective DA reuptake inhibitor), nisoxetine (a selective NE reuptake inhibitor) or combinations of GBR12783 and nisoxetine. All three decreased food intake in lean or obese mice. However, the combination of the two selective agents produced an additive reduction in body weight gain, suggesting that both catecholamines play a role in Bupropion's effects on energy balance.*' As Bupropion was not used in combination with either selective agent, the abovementioned statement does not support the hypothetical additive or synergistic effect of Bupropion in the NB combination.

Non-clinical literature presented by the Applicant suggests that Bupropion increases energy expenditure in rodents by increasing thermogenesis and locomotor activity.

Secondary pharmacodynamic effects of Bupropion in rodents include anti-nociception in mechanical allodynia, decreased prolactin concentrations, and decreased baseline gastric secretion and produces subjective and reinforcing effects in the context of abuse potential assessment.

The studies cited by the Applicant supporting the pharmacodynamic properties of Naltrexone Bupropion provide somewhat contradicting data on the anorexic properties of the drug. Nevertheless, the rationale for not performing new non-clinical studies is however supported in this case due to the results from the clinical studies.

NB combination

The proposed mechanism of action of NB combination for the treatment of obesity is based on basic research on regulation of food intake by the hypothalamus and reward centres of the brain.

No new non-clinical studies have been performed by the Applicant to support the NB combination, but literature references showing the effects of Naltrexone and Bupropion, combined and alone, as well as the combination of Bupropion+Naltrexone and other drugs have been cited.

The intended route of administration for NB is via oral route, however, most PD studies presented by the Applicant report IP or SC dosing. This can be acceptable, as the bioavailability following oral administration gives rise to similar exposure values as following IP or SC administration.

Only two studies were presented investigating repeated administration of NB in mice and rats and these were by the same authors in the same paper (Clapper et al., 2013). In the acute studies, Naltrexone and Bupropion did indeed have an inhibitory effect on diet consumption in both diet induced obese (DIO) mice as well as in lean mice fed high fat diet, however, by 4 hours post treatment, no differences was observed compared to saline control. In the repeat-dose study in DIO rats' diet consumption was reduced following as well as body weight and fat mass in Naltrexone/Bupropion treated animals compared to vehicle. Additive effect of NB on food intake and weight loss in mice was found at 1 and 50 mg/kg Naltrexone and Bupropion, respectively, and in rats at 1 and 20 mg/kg Naltrexone and Bupropion, respectively. These doses correspond to human doses of 8.0 and 3.2 mg/kg based on body surface area conversion.

In the study by Clapper et al. (2013), a significant reduction of POMC mRNA expression (approximately 40%) was found after 14 days treatment with the NB combination. In addition, no change in MC4R mRNA expression was found after NB treatment. These results contradict the proposed mechanism of action of NB by the Applicant as well as results from e.g. Greenway et al. (2009), in which the firing rate of hypothalamic POMC neurons was increased after administration of NB.

Safety pharmacology programme

Naltrexone

Cardiovascular effects / HERG study

For the metabolite, 6-Beta Naltrexol, a dilution error had occurred in the hERG study conducted by the Applicant, so the concentration of 0.1 µM 6-Beta Naltrexol was not tested. When looking at the data from the study, it seems convincing that both Naltrexone and the metabolite 6-Beta Naltrexol inhibit hERG mediated potassium currents by increasing concentrations. Previous in vitro work conducted to evaluate bupropion effects on several inwardly rectifying potassium channels in vitro demonstrated minimal effects. Therefore, a combination hERG assay was deemed unnecessary, consistent with the EMEA/CHMP/SWP/258498/2005 guideline on the nonclinical development of fixed combinations of medicinal products.

It is correctly referred that 'no effect of Naltrexone (20 mg/kg/day) on heart rate or mean arterial pressure in sham operated rats was found under baseline conditions in the study by Tavakoli et al. (2007). However, ICH guideline S7B states: 'The ionic mechanisms of repolarisation in adult rats and mice differ from larger species, including humans (the primary ion currents controlling repolarisation in adult rats and mice is Ito); therefore, use of these species is not considered appropriate.' Therefore,

the data on Naltrexone in the abovementioned study are not fully relevant to support the safety pharmacology of Naltrexone. The clinical data from the clinical use of Naltrexone indication are rather addressing this concern.

The transient increase in blood pressure following 10 mg/kg Naltrexone in the study by Byrd (1983) was discussed by the author: '*The transient increase in blood pressure after 10.0 mg/kg naloxone or Naltrexone may have been due indirectly to behavioural changes precipitated by this dose rather than to direct effects on the cardiovascular system. Most of the monkeys displayed unusual behavioural including retching, vomiting, and profuse salivation and frothing after 10.0 mg/kg, and the periodic muscular contractions associated with these activities may have produced the transient increases in pressure.*' Based on this, in this study, the transient increase in blood pressure seen in the 10 mg/kg IV dose group is not considered a potential safety issue for Naltrexone.

Bupropion

Cardiovascular effects of Bupropion have been investigated in several experimental systems.

Ex vivo: In rat and guinea pig atria, Bupropion at and above 10 µM decreased sinus rate. In canine Purkinje fibres, a slight depolarisation in resting membrane potential was seen at concentrations of 100 µM Bupropion. In a hERG study, Bupropion functioned as a weak IKr blocker with an estimated IC50 on hERG tail currents of approximately 34 µM. In isolated guinea-pig hearts 10 µM Bupropion caused mild QRS widening. Bupropion may further inhibit gap function intercellular communication.

In vivo: In anaesthetised dogs, 3-6 mg/kg Bupropion IV transiently increased pulmonary vascular resistance index and mean pulmonary arterial pressure while no effect on other cardiovascular parameters was found. The validity of these results seems authentic, however, potential bias from use of pentobarbital cannot be ruled out. Using e.g. the FEAB model would have been preferable for this kind of study, as one of its major characteristics is its ability to maintain homeostatic cardiovascular reflexes that are comparable to those of normal conscious animals. The dose-dependent pro- and/or anticonvulsant properties of Bupropion have been investigated in a relatively large number of non-clinical studies, mainly investigating the seizure threshold lowering or increasing capacity of Bupropion when administered before or together with other substances with convulsive properties.

The CD50 values reported by various authors in mice range from 82-157 mg/kg Bupropion IP. As argued by the Applicant, the lowest value of 82 mg/kg may represent an underestimation and so the Applicant states that '*in all studies, convulsions have been reported at doses largely exceeding the proposed clinical dose (on a mg/kg body weight basis) for NB*.' This statement cannot be supported, as a CD50 of 157 mg/kg (highest value reported) corresponds to (157/12.3) = 12.8 mg/kg. Bupropion is not even 2-fold higher than the dose proposed for NB (7.2 mg/kg based on standard weight of 50 kg for an adult). However, as seizures were only reported to occur at an incidence of 0.1 % in the clinical studies of NB, and use of NB is contraindicated in individuals with a seizure disorder or a history of seizures, the lack of a greater safety margin is acceptable.

2.3.3. Pharmacokinetics

No new single dose pharmacokinetic studies have been performed with the NB combination. The non-clinical pharmacokinetics of Naltrexone and Bupropion is summarised as a series of literature studies. It cannot be verified from the publications that the studies described would conform to current Good Laboratory Practices (GLP) standards. It also cannot be confirmed from the literature reports whether pharmacokinetic studies were conducted with the active pharmaceutical ingredients conforming to current standards and no information is provided in the publications with respect to the impurity or degradant profiles of lots used.

Some of the analytical methods (e.g. TLC) are considered old compared to today and furthermore, on some occasions information is missing regarding Limit of Detection. However, in general the analytical methods used are considered acceptable.

Absorption

The lack of multiple dose nonclinical PK data for naltrexone is acceptable, as clinical PK data demonstrate that naltrexone is well-absorbed, widely distributed and extensively metabolised through hepatic and extra-hepatic mechanisms after oral administration. Clinical data also demonstrate dose-proportionality of naltrexone and no time-dependent effects.

Adequate information is available regarding the absorption of Bupropion after PO and IV administration. The time dependency of the Pharmacokinetics of Bupropion and its primary metabolite (Hydroxybupropion) is discussed for three different animal species. No published data was provided on dose proportionality of bupropion or its hydroxybupropion metabolite in non-clinical models. This is acceptable, as clinical data for the AUC and C_{max} of bupropion and its active metabolites hydroxybupropion and threohydrobupropion are available from clinical studies.

Distribution

The results of the autoradiography revealed rapid distribution from plasma to body tissues. High radioactivity was observed in the elimination organs (*e.g. kidney and liver*) and furthermore in the lung, testis and spleen. The highest Naltrexone concentration was observed in sub maxillary gland in the rabbit 1.5 hr post administration. Detectable radioactivity could be observed in brain and plasma 96 hours post dosing.

The presented literature data are in general considered acceptable in order to evaluate the tissue distribution of Bupropion. The result of the literature tissue distribution study reveals that Bupropion is widely distributed in body tissue. The majority of the parent compound and its metabolites are primarily distributed to the elimination organs (*e.g. liver and kidney*).

Metabolism

The provided information regarding metabolic fate of Naltrexone and domination metabolites in animals and humans are in general considered acceptable. Concentration time relationship of the different metabolites in biological matrices is presented.

The pre-systemic metabolism is discussed (*hepatic first pass effect*). The primary products of metabolism of Naltrexone in animals are conjugated Naltrexone and free and conjugated forms of 6β-naltrexol. In humans the enzyme responsible for the formation of the primary metabolite 6β-naltrexol is described as dihydrodiol dehydrogenases, however, no mechanism is proposed for the discussed animal species.

Bupropion has been shown to induce its own metabolism (*auto induction*). Hydroxybupropion is considered the most important metabolite of Bupropion, as it is pharmacologically active. The provided information regarding metabolic fate of Bupropion to Hydroxybupropion in humans and animals is considered acceptable. In humans CYP2B6 is considered the primary enzyme responsible for the metabolism and in animals (rats) it is CYP2B1 (*75% homolog to CYP2B6*). The Applicant has provided a table (Welch 1987) which includes a summary of the mean systemic exposure of bupropion and its hydroxybupropion metabolite following single and multiple oral dose administration of bupropion in mouse, rat and dog. This information is sufficient to address the species differences in the relative proportion of circulating bupropion to hydroxybupropion.

The pre-systemic metabolism of Bupropion is discussed in relation to the gastrointestinal system in rats. Based on in vitro affinity studies, different enzymes (*CYP2C11 and CYP2E1*) are suggested to be responsible for the metabolism of Bupropion to Hydroxybupropion in rats.

Elimination

With regards to the excretion of Naltrexone, the literature data provided are in general considered acceptable. Mass balance studies shows that Naltrexone and its metabolite are almost completely eliminated in urine and faeces. Differences exist between animal species. Data obtained from monkeys are considered more similar to humans. However, caution should be made with interpretation of the enclosed data as different dose levels were administered and different routes of administration were used.

Literature study data are presented of Bupropion excretion. Mass balance studies show that Bupropion and its metabolite are almost completely eliminated in urine and faeces. Less than 1% of the radioactivity was excreted in the urine or faeces as unchanged parent compound. It should be noted that only one animal species is discussed and that no comparison is made to humans.

Drug interactions

In humans the enzyme responsible for the biotransformation of Naltrexone to the primary metabolite 6β-naltrexol is described as dihydrodiol dehydrogenases and for Bupropion CYP2B6 is considered the primary enzyme responsible for its metabolism/biotransformation into its active metabolite Hydroxybupropion. Therefore, the risk for clinical relevant drug interactions with concomitant use is considered minimal.

There are no known significant drug interactions involving monotherapy with Naltrexone. However, there is a potential for drug interactions with Bupropion because of its extensive metabolism, especially with agents that are metabolised by the CYP2B6 isoenzyme.

Bupropion and its metabolites showed nearly 100% inhibition of the OCT2 transporter at the highest concentrations (220, 2000 and 1000 µM for Bupropion, hydroxybupropion and a mix of hydroxybuprion and erythrohydrobuproprion respectively).

Neither Naltrexone (0.003-2.200 µM), nor 6β-naltrexone (0.08–60 µM) showed a clinically relevant potential for interference with the OCT2 uptake transporter. Naltrexone did not inhibit the human OCT2-mediated metformin uptake, and 6β-naltrexol showed only modest dose-dependent inhibitory effect at the highest concentration. The presented information regarding drug-drug interaction at the active drug transporter level is considered adequate and reveals that no interaction occurs at the primary active transporter of Bupropion (hOCT2). No interaction is therefore expected at the active carrier of hOCT2.

2.3.4. Toxicology

The non-clinical toxicology of Naltrexone and Bupropion is summarised as a series of literature studies. Supportive information is made from the summary of product characteristics (SmPCs) and from the prescribing information of the marketed products, Adepend®, ReVia®, Vivitrol® and Wellbutin®. It cannot be verified from the publications that the published studies described conform to Good Laboratory Practices (GLP) standards. It also cannot be confirmed from the literature reports whether toxicity studies were conducted with the active pharmaceutical ingredients conforming to current standards and no information is provided in the publications with respect to the impurity or degradant profiles of batches/lots used. Only very few *in vivo* studies of more recent date included analysis of exposure/response relationships, so only limited toxicokinetic information is available for Naltrexone and Bupropion.

It should be noted that none of the literature sources included estimates for the no adverse effect level (NOAEL), so where possible, NOAEL values for the data presented in the cited articles have been estimated by the Applicant.

2.3.4.1. Naltrexone

Single dose toxicity

Single dose toxicity studies of Naltrexone were conducted in several species, and LD50 values following PO dosing were in the range of >1000 mg/kg (rat, mouse and monkey) and 130 mg/kg in dogs. The majority of clinical signs of acute toxicity included central nervous system depression, retching/emesis, salivation, convulsions and death.

Repeat dose toxicity

In a two-year chronic rat study with Naltrexone administered PO (0, 10, 30 and 100 mg/kg/day; Braude and Morrison, 1976) a high spontaneous mortality rate (>50%) was found in both Naltrexone treated animals and controls. The cause of death in most animals was inflammatory lesions of the respiratory system due to chronic murine pneumonia and acute bronchopneumonia, resulting in respiratory failure. Some animals had acute inflammatory lesions in other organs which were probably due to haematogenous dissemination of the infection from the lungs. The conclusion from the authors was that *'no toxic signs that could be attributed to the test drug were found in the study'*. However, the high prevalence of murine respiratory disease with resultant high spontaneous mortality rates from around week 18, resulted in decreasing group sizes which further complicates statistical calculations and study validity. The results from this study should therefore be used with caution, as the data are likely to be biased.

In two repeat-dose studies of Naltrexone (90 d PO dogs and 90 d PO rat) described in Braude and Morrison (1976), increases in absolute organ weights and/or percent of body weight ratios were described in the reference. It is not described which organs are involved, the number of animals/dose groups affected and the word 'slight' does not clarify any quantitative measure.

In a 1-year oral toxicity study in monkeys with Naltrexone doses of 0, 6, 12, 24/18 and 72 mg/kg/day, Naltrexone was poorly tolerated in the initial phase of dosing for most doses. This was due to a 'reaction syndrome' which appeared in the initial phase of the study. The animals showed an appetite loss which resulted in a sharp decrease or halt in food consumption, followed by weight loss. The syndrome progressed to mucoid rhinitis, haemorrhagic colitis and respiratory infections – ultimately resulting in the death of the affected animals. The study was re-designed to include removal of the high dose (72 mg/kg/day), reduction of the next lower dose (from 24 to 18 mg/kg/day), and institution of temporary dosing reductions and addition of a 12 mg/kg/day group with initial titration. It was concluded that repeated dosing in monkeys was feasible and that the 12 mg/kg/day dose produced no adverse effects when initial dose titration was used.

NOAEL´s following repeated administration of Naltrexone were estimated by the Applicant from the available literature as follows:

Mouse: 3000 mg/kg (in feed, 90 days)

Rat: 300 mg/kg (SC, 30 days); 70 mg/kg (PO, 90 days); 30 mg/kg (PO, 2y)

Dog: 20 mg/kg (PO, 90 days); 10 mg/kg (SC, 30 days)

Monkey: 126 mg/kg (PO, 3-7 days); 12 mg/kg (PO, 2 years); 20 (PO, 1 year)

Genotoxicity

Brusick et al (1978) thoroughly described the genotoxic potential of Naltrexone, by testing Naltrexone in a series of in vitro and in vivo tests. The test battery included tests for point mutations, TK+/- forward mutation in mouse lymphoma cells, assay for unscheduled DNA synthesis in WI-38 cells and chromosome damage, bone marrow cytogeneic analysis in rats and an assay in mice for detecting

heritable translocations. The Authors concluded that there does not appear to be any significant genetic hazard associated with the use of Naltrexone in drug abuse treatment. This conclusion was reached, even though Naltrexone produced signs of positive results in some bacterial tests (e.g. *E.coli* and *S. typhimurium* strain TA-1538), as well as in the unscheduled DNA synthesis test. The genotoxicity results appear to be best reflected in the Vivitrol prescribing information, and the Applicant has aligned the SmPC text accordingly.

Carcinogenicity

Some mechanistic studies reported in the literature have employed Naltrexone as a research tool. However, contrasting results have been obtained, where in one study Naltrexone stimulated cell proliferation of neuroblastoma cells (Zagon and McLaughlin, 1990), whereas in another study, Naltrexone reduced the incidence of tumours in a stress induced model of mammary tumourigenesis in rats (Tejwani et al, 1991). The latter result was supported by Koo et al (1996). The significance of these results has not been discussed further. This is however acceptable considering the additional supportive data below.

As supportive to the above literature data, the Applicant refers to the ReVia® product labelling, describing carcinogenicity studies of Naltrexone in mice and rats. The original literature of these studies is not available according to the applicant. However, in the rat study, the incidence of mesotheliomas and vascular tumours was 6% (males, 100 mg/kg/day), reported to be slightly higher than the maximum historical incidence (4%).

Reproduction Toxicity

The UK SmPC for Naltrexone hydrochloride states that in rats, 100 mg/kg caused a significant increase in pseudo pregnancy and a decrease in the pregnancy rate at 100 mg/kg/day. A decrease in the pregnancy rate of mated female rats also occurred. The relevance of these observations to human fertility is not known (Adepend®).

Fertility and early embryonic development was studied in rats (Christian et al., 1984). Animals were administered PO daily doses of 10, 30 or 100 mg/kg/day of Naltrexone for 63 days prior to mating and during a 21-day mating period (males) or for 14 days prior to mating, during mating, and until termination (females). Treatment with ≥ 30 mg/kg Naltrexone resulted in excess grooming, hyper reactivity and hypersensitivity (females only), and increased stillbirths. 100 mg/kg Naltrexone increased incidence of pseudo pregnancy and decreased fertility as well as transient body weight decreases were observed. The US prescribing information for Revia® also states that Naltrexone has been shown to increase the incidence of early foetal loss when given to rats at doses ≥ 30 mg/kg/day and to rabbits at oral doses ≥ 50 mg/kg/day. There was no evidence of teratogenicity when Naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (ReVia® prescribing information).

Embryo-foetal development has been studied in rats and rabbits (Christian et al., 1984). Rats and rabbits were treated with 0, 20, 60 and 200 mg/kg Naltrexone from gestation day 6 to 15 and 18 (rat and rabbit respectively). Maternal toxicity consisted mainly of transiently decreased bodyweight gain, observed in both species in the high dose groups, but only in rats at 60 mg/kg/day. In all treated groups rats displayed hyper-reactivity and vocalisation, violent twisting of the body during dosing and chromorhinorrhoea in mid and high dose, and excess salivation, ptosis and red discharge from the mouth and convulsions at 200 mg/kg. In rabbits, non-significant increased foetal resorption was observed at 200 mg/kg/day. No other maternal toxicity, apart from the transiently decreased body weight gain in the high dose group was observed in the rabbits. NOAEL for maternal toxicity was considered to be 20 and 200 mg/kg/day for rats and rabbits respectively. As no effects were observed in foetal parameters of the two studies, the foetal NOAEL was considered to be >200 mg/kg/day.

Local tolerance

Since Naltrexone has been used extensively by individuals via the oral route for many years at comparable dose levels to 32 mg Naltrexone in NB, there is no requirement for local tolerance investigations. Furthermore, information on local tolerance in toxicity species has been provided for the individual drug substances and from clinical studies using NB.

Other toxicity studies

An impurity of Naltrexone was identified which possesses a potentially genotoxic structural alert feature, but was shown to be negative in the AMES Mutagenicity test. This impurity is controlled by a validated LC/MS analytical test method. In addition to this impurity, other naltrexone impurities were negative in Ames tests.

Naltrexone (30 mg/kg IP for 7 days) increases cell proliferation of basal epithelial cells of the cornea and other ocular tissues (Zagon et al. 2006). The proliferative effects of Naltrexone were, however, not termed pathologic or toxicological by the authors. Published literature on toxicity studies with Naltrexone provides no evidence of ocular toxicity. The clinical significance of this finding has not been discussed by the Applicant and this is acceptable as long as no such signs have been observed in the clinical setting.

Cheng et al. (2009) reported that Naltrexone likely enters carcinoma cells by passive diffusion, and increases DNA synthesis. The clinical relevance of the observed increase in DNA synthesis is unclear. As rat carcinogenicity studies have demonstrated a slight increase in tumour formation compared to historical controls, it could be hypothesised that an increase in DNA synthesis by Naltrexone could be of clinical importance in development of neoplasm's in humans, but the clinical risk of this is unknown.

2.3.4.2. Bupropion

Single dose toxicity

Single dose toxicity studies of Bupropion were conducted in mice with LD50 values 544-636 mg/kg and 273 mg/kg for PO and IP dosing, respectively. The LD50 values in rats were 482-607 mg/kg and 263 mg/kg for PO and IP dosing, respectively. The majority of clinical signs of acute toxicity included ataxia, clonic convulsions, prostration, laboured breathing, salivation, arched back and ptosis and death.

Repeat dose toxicity

Repeat-dose toxicity studies in rats were reported for 12, 26 and 55 weeks duration. PO doses of 25-450 mg/kg/day resulted in dose-related urinary incontinence, irritability, excessive salivation and intermittent convulsions (at doses of >200 mg/kg/day). At all dose levels, increased liver weights due to enzyme induction was found and increased relative kidney weights at 100 mg/kg/day was found in the 55-week study. No treatment-related effects were noted for haematology, clinical chemistry and urinalysis parameters, ophthalmological examination and gross and microscopic examination. NOAEL levels were estimated by the Applicant to be ≤150 mg/kg/day (12-week study), 100 mg/kg/day (26-week study) and ≤25 mg/kg/day (55-week study) and these levels are found to be reasonably estimated.

NOAEL estimated in the 12-week study of 150 mg/kg/day resulted in significant toxicological signs in a subsequent 52-week study in dogs. In this study, NOAEL was estimated to be 40 mg/kg/day. Chronic (52-week) PO administration of 80-150 mg/kg/day Bupropion to dogs produced mild, transient and reversible hepatotoxicity.

Genotoxicity

No new genotoxicity studies for the NB combination have been made by the Applicant. Bupropion tested 'borderline positive´ (1-3 times control mutation rate) in 2 of 5 bacterial strains in the Ames mutagenesis assay, however, the concentrations applied were not described. An increase was also found in chromosome damage at 300 mg/kg/day Bupropion (PO for 5 days) in a rat study.

Carcinogenicity

In carcinogenicity studies in mice, a dose-related increase in the incidence of dilated blood vessels in the uterus was found after PO dosing with Bupropion (50, 100 and 150 mg/kg/day for 96 weeks). No treatment-related effect on tumour incidence was found.

In a rat carcinogenicity study, PO dosing with Bupropion (100, 200 and 300 mg/kg/day for 104 weeks) resulted in dose-related increases in liver weight, hepatocellular hypertrophy and focal nodular hyperplasia of hepatocytes at all dose levels.

Reproduction toxicity

Fertility and general reproduction was investigated in rats receiving Bupropion PO (100, 200 or 300 mg/kg/day; Males: 60 days prior to mating and Females: 15 days prior to mating, through gestation and lactation). F1 offspring were mated. NOAEL for maternal toxicity was set to 100 mg/kg/day and no effects on fertility or reproductive parameters of the parent or offspring, the mated F1 generation or their offspring.

In an embryo-fetal development study, maternal toxicity of Bupropion occurred at doses ≥300 mg/kg/day (PO) in rats and at 100 and 150 mg/kg/day in rabbits. NOAEL´s for maternal toxicity were determined to be 150 and 50 mg/kg/day in rats and rabbits, respectively. No clear evidence of teratogenic activity in rats or rabbits dosed PO up to 450 mg/kg/day and 150 mg/kg/day, respectively. However, in rabbits slightly increased incidences of fetal malformations and skeletal variations were observed at greater than or equal to the lowest dose tested (25 mg/kg/day, 1.1-fold of the MRHD in NB).

SC dosing of Bupropion (5 and 10 mg/kg/day) to female Wistar rats 14 days prior to mating and during pregnancy until weaning (PND21) was investigated by DeLong et al. (2013). There was no effect of either dose of Bupropion on mating or pregnancy success, time to pregnancy, gestation length, the live birth index, litter size, sex ratio, survival to PND4 or survival to weaning. Birth weight in the offspring of dams treated with 10 mg/kg was significantly reduced compared to controls (5.9 ± 0.2 g versus 6.7 ± 0.2 g; p=0.02). Bupropion exposure during pregnancy resulted in advanced vaginal opening (e.g. earlier pubertal onset) in the female F1 offspring, but only at the 10 mg/kg/day dose. At 6 months of age, no effects on time to pregnancy, gestation length, mating or pregnancy success, live birth index, litter size birth weight, sex ratio, postnatal survival to either PND4 or weaning were reported. The F2 offspring of females exposed to 10 mg/kg Bupropion in uterus and during lactation also experienced an earlier onset of puberty (age at vaginal opening) relative to control animals. The NOAEL for the offspring in the study was 5 mg/kg/day. No adverse maternal or reproductive effects were noted in the study at 5 or 10 mg/kg/day (DeLong et al., 2013).

In rats receiving Bupropion (15 mg/kg/day SC) from PND8 to PND21, sensory and social abnormalities were found.

Local Tolerance

Since Bupropion has been used extensively via the oral route over many years at comparable dose levels to 360 mg Bupropion in NB, there is no requirement for local tolerance investigations.

2-Bromo-3'-chloropropiophenone (BCP) has been identified as an impurity of Bupropion. BCP was found to be mutagenic with S9 metabolic activation in the Ames test (up to 22- and 145-fold induction over controls) and was found positive in the in vitro micronucleus assay (3.3-5.1-fold increase in frequency and 9.9- and 7.4-increase of aneuploidies without and with S9, respectively). BCP was found to induce formation of reactive oxygen species in TK6 cells.

A specification of NMT 4 ppm was set based on the genotoxic potential of BCP from structural considerations. For a potentially genotoxic impurity, EMEA/CHMP/QWP/251344/2006 states a limit of NMT 1.5 µg/day, which based on the proposed Bupropion dosing regimen of 360 mg/day corresponds to [(1.5)(106)] / [(360)(1000)] = 4 ppm 2-bromo-3'-chloropropiophenone which is found to be acceptable for the current application.

2.3.5. Ecotoxicity / environmental risk assessment

The proposed indication will entail an increase in the environmental concentration of both Naltrexone and Bupropion, as the approval of the combination therapy will be used in a different population to the already approved Bupropion and Naltrexone respectively. Buproprion is approved as an aid in smoking cessation at doses of 300 mg/day for up to 7-9 weeks (Zyban), or as an antidepressant (Wellbutrin) at 300 mg/day (or up to a maximum of 400 mg/day). Naltrexone is approved as a treatment against alcoholism (Adepend) at 50 mg/day. As the approval of the NB combination is in a new population an increase in the use of both compounds, and consequently in the exposure of the environment, a new environmental assessment is required. The Applicant has initiated and completed studies for Bupropion, however, some studies remain to be performed. For Naltrexone the Applicant has not performed any studies yet, but has planned to perform studies, and the results will provide the basis for an environmental risk assessment. The calculated PECsurfacewater has been calculated based on Fpen based on predicted sales forecasts and the highest yearly expected sales (from year 7 after approval).

The Applicant proposes to perform an OECD 302 study to confirm that Bupropion is indeed inherently biodegradable, and hence if this study confirms the previously reported results, not perform an OECD 308 study. This approach is not acceptable, as according to Q&A on the guideline on environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010) it is explicitly described that only a result from an OECD 301 that a compound is readily biodegradable, can be used to waive an OECD 308 study. Therefore, the Applicant is asked to perform an OECD 308 study if it cannot be determined that the Bupropion is ready biodegradable (by an OECD 301 study). In addition the Applicant is asked to conduct a bioaccumulation study according to OECD 305 in the Phase II assessment, as the logKow of Buproprion is 3.18 at pH 9 (e.g. above 3).

Bupropion: No values are above the trigger, and no further analysis is required. However, the planned studies for Bupropion still need to be performed, and the results need to be assessed to establish if the new results will impact the Tier A assessment.

Naltrexone: the environmental risk assessment cannot be completed at present, as the studies are not yet completed, and therefore no results are available. The Applicant should send the study reports and an updated ERA upon completion of the planned studies.

Prior to the Applicant having performed and submitted the studies, a definite conclusion regarding the environmental risk assessment cannot be made. The Applicant should send the study reports and an updated ERA upon completion of the planned studies as part of a post approval commitment.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Naltrexone and Bupropion to the environment. Nevertheless, the available results are summarised below.

Summary of main study results

Substance (INN / Invented Name): naltrexone					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Estimated	1.92			Potential PBT (N) However, this needs to be confirmed experimentally
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.92			not B, however, this remains to be confirmed experimentally
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0061	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Planned but not conducted yet			To be completed
Ready Biodegradability Test	OECD 301	Planned but not conducted yet			To be completed
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	To be performed, dependent on the results obtained in OECD 301			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	Not performed yet. Will be submitted when report is available
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	Not performed yet. Will be submitted when report is available
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Not performed yet. Will be submitted when report is available
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	Not performed yet. Will be submitted when report is available
Phase IIb Studies - to be completed if the results from the planned OECD 106 study on adsorption-Desorption					

Summary of main study results for buproprion (Bupropion)

Substance (INN / Invented Name): buproprion			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5: -0.207 pH 7: 1.83 pH 9: 3.18	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5: -0.207 pH 7: 1.83 pH 9: 3.18	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB		

	The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.068	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Planned but not conducted yet			To be completed
Ready Biodegradability Test	OECD 301	1.21 % in 14 days			Not ready biodegradable
Ready biodegradability test	OECD 301B	0.2 – 1.0 % CO2			Not ready biodegradable
Inherent biodegradability	OECD 302	90 % in 14 days			Inherent biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella sucapitata* *Scenedesmus subspicatus* (Wellbutrin monograph FASS.se)	OECD 201	NOEC	11.1 620	µg/L	The two different species used show quite different sensitivity
Acute toxicity 24 and 48 h *Daphnia magna*	OECD 202	EC_{50} 24 h EC_{50} 48h NOEC 48h LOEC 48h	>10 7.5 5.0 10	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	Planned but not conducted yet
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	100	µg/L	Results obtained from Wellbutrin monograph, Applicant propose to perform a GLP compliant OECD 201 study and provide results when available
Acute toxicity *Pimephales promelas*	-	NOEC 96h	5.0	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC 30 min	196.6	mg/L	
Phase IIb Studies – to be completed if the results from the planned OECD 106 study on adsorption-Desorption					

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

The Applicant is requested to perform all the planned studies for the environmental risk assessment for bupropion (e.g. OECD 106, 210 and 211) and naltrexone (OECD 106, 201, 209, 210, 211 and 301) as well as OECD 308 for both compounds, should the results from the respective OECD 301 studies deem this necessary.

2.3.6. Discussion on non-clinical aspects

The applicant provided literature data supplemented by non-clinical studies to support the non-clinical part of the application.

The pharmacodynamic studies cited by the Applicant provide somewhat contradicting data on the anorexic properties of Naltrexone. This may be reflected in several issues, e.g. that the exact mechanism of action of Naltrexone has not been completely elucidated, the end point reported is

mainly reduced food intake (transient) and not weight loss, and that no study is presented in this section with the specific aim of investigating the anorexic effects of Naltrexone (as e.g. Clapper et al., 2013). In light of the anorexic effects demonstrated in the clinical studies with NB, the lack of new non-clinical studies is supported.

The Applicant refers to the PD/PK and toxicology stated for Naltrexone in the SmPC of Nalorex® and Adepend® and for Bupropion in the Wellbutinin® SmPC and prescribing information addition to published literature on pharmacodynamic effects of both compounds. Generally, the data from the literature of Naltrexone and Bupropion is correct and comprehensive and support the current application and include a discussion on the studies that do not support the proposed indication.

Cardiovascular effects of naltrexone and Bupropion have been investigated in several experimental systems, including hERG studies which so not show a concern.

No new toxicity studies have been performed with the NB combination. The Applicant has provided a discussion regarding several factors relevant to the safety of the NB combination to elaborate on the lack of a bridging study with the NB combination. Based on this discussion, the lack of a 3-month repeat dose toxicity (bridging) study with the NB combination is accepted.

The lack of any reproductive toxicity studies for the NB combination is acceptable, as literature data on the developmental toxicity of both compounds following monotherapy exists, and the use of NB combination in pregnancy is discouraged in the SmPC.

The lack of any studies with NB on juvenile animals is acceptable as it is not planned to be used in children until further studies have been performed following development of a suited formulation. A PIP is approved by EMA and the details can be found in the following document on the EMA web page: P/0188/2013.

The toxicology of bupropion is described by the applicant based on literature data and has been appropriately discussed.

Braude et al. (1976) is one of the major references used by the Applicant to describe the toxicology of Naltrexone. This paper summarises toxicological effects of Naltrexone in multiple study set-ups, in several animal species and approximately ten studies are described to varying degree. The paper gives a good overview of the toxicology of Naltrexone in different studies and animal species (rat, rabbit, dog and monkey), however, the description of toxicological effects seems somewhat subjective and are not supported by references to the original work, e.g. materials, methods, number of animals (in some cases) and results (tables and figures). In addition, many descriptions of toxicological effects are un-precise, e.g. ‘a slight increase in a few absolute organ weights and/or percent of body weight ratios’ and ‘minor abnormalities in the lungs’, where it is reasonable to ask: which organs and what kind of abnormalities, respectively. The information obtained from this source is, however, considered to be in line with other studies investigating toxicology of Naltrexone, and together with the large amount of clinical data on Naltrexone through the past years, the reference is considered acceptable for use in the current application for NB.

Although Naltrexone has been used clinically for many years, the potential of NB to induce hepatotoxicity in chronic treatment cannot be ruled out. In addition, liver changes have been described in animals after treatment with Bupropion (SPC NB p.17), so it is considered appropriate to keep the wording in the SPC for NB (p.3) that caution should be taken when administering NB to individuals with hepatic impairment and that NB is contraindicated in individuals with severe hepatic disease.

The genotoxicity of naltrexone is detailed in a publication and considered adequate. The amount of data describing the genotoxicity of Bupropion is somewhat small and the present application concerns a chronic treatment regimen, whereas the indication for Bupropion as monotherapy is of shorter

dosing duration. In the D120 response to the LoQ, the Applicant has thoroughly discussed the potential genotoxic effects of bupropion in long-term treatment. It is acknowledged that the rat study showing chromosome damage (Tucker et al., 1987) is lacking in experimental detail and that other studies, as well as the FDA review of Zyban, indicate that bupropion at single doses of 125-500 mg/day to rats does not induce chromosome damage. This is strengthened by the lack of tumorigenicity in lifetime rodent carcinogenicity studies of bupropion. Therefore this is acceptable to the CHMP.

The Applicant presented two pre- and postnatal development studies performed in rats. Christian (1984) administered 0, 10, 30 and 100 mg/kg/day PO from gestation day 15 whereas Farid et al (2012) implanted a sustained release implant subcutaneously which resulted in plasma exposure of 0.3-9.7 ng/mL in the dams. In the first reference, no effects were observed on any litter parameters, but maternal body weight gain was decreased, transiently in the low dose group, but persistently so in 30 and 100 mg/kg/day. Therefore a maternal NOAEL of 10 mg/kg/day was established in this study, whereas the fetal NOAEL was considered to be >100 mg/kg/day. The study by Farid et al (2012) was designed to examine the effects of maternally administered sustained release Naltrexone in rats on offspring neurochemistry and behaviour in adulthood. The authors concluded that chronic low-dose maternal Naltrexone delivered via a sustained release implant impacts behaviour and neurochemistry in adult offspring, without obvious morphological effects. Compared to placebo, basal motor activity of Naltrexone-exposed adult offspring was lower, yet showed enhanced development of psychomotor sensitisation to morphine. The discrepancy between Christian (1984) not discovering any detrimental effects to the embryo-fetal development and Farid et al (2012) establishing that even low dose chronic exposure of the fetus will result in lasting effects on the offspring, highlights the need for specific studies when the compound has effects in the CNS. The SmPC text currently states that NB is not recommended during pregnancy, which is considered appropriate given the contradicting results of the abovementioned studies.

In summary, the applicant´s approach to perform only 3 nonclinical studies in support of the current application is acceptable, as there is sufficient relevant literature that can provide evidence that the combination of Naltrexone and Bupropion in the new proposed indication is efficacious and safe.

The fact that both compounds are approved and have been used clinically for a number of years is reassuring, as the safety profile of each drug is well known and can provide further supportive evidence to the non-clinical data. However, the drugs have not been used in combination, or in the proposed indication for management of obesity and weight-loss and maintenance of weight-loss.

2.3.7. Conclusion on non-clinical aspects

From a non-clinical perspective, Naltrexone/Bupropion can be approved.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The list of studies submitted is detailed below:

Study Number	Objective / Design	Study Treatment and Dose (mg/day)[a]
NB-221	Safety, tolerability and PK of IR and PR NAL in healthy obese subjects Double-Blind, Crossover	NAL IR 36 mg NAL PR 40 mg (fed; 2 hours before dosing)
NB-225	PK, safety and tolerability of multiple-dose NAL PR plus BUP PR, and NAL IR plus BUP PR in healthy obese subjects Double-Blind, Parallel	NAL PR 37.5 mg/BUP PR 270 mg (NB 37.5) NAL IR 36 mg /BUP PR 270 mg (NB 36) (fasted)
NB-228	Assess relative BA of NB 8/90 tablets prepared under different manufacturing schemes in fasted adult subjects Open-Label, Crossover	NAL PR 16 mg + BUP PR 180 mg trilayer NAL PR 16 mg + BUP PR 180 mg trilayer (fasted)
NB-229	Assess the relative BA of NB 8/90 mg tablets prepared under different manufacturing schemes in healthy adult subjects. Open-Label, Crossover	NAL PR 16 mg + BUP PR 180 mg trilayer (fasted)
NB-230	Assess the relative BA of NB 8/90 tablets to commercially available tablet formulations of NAL IR and BUP PR in Healthy Adult subjects. Open-Label, Crossover	NAL PR 16 mg + BUP PR 180 mg NAL IR 50 mg (Barr) BUP PR 150 mg (Sandoz) (fasted)
NB-231	Assess the relative BA of three NAL PR/ BUP PR combination monolayer tablet formulations to NB 8/90 tablets in healthy adults. Open-Label, Crossover	NAL PR 16 mg + BUP PR 180 mg (fasted)
NB-232	Assess the effects of atorvastatin or valsartan on the PK of NB 8/90 tablets, and to determine the relative BA of NB 4/90 and NB 8/90 tablets in healthy adults. Open-Label, Crossover	NAL PR 8 mg + BUP PR 180 mg NAL PR 16 mg + BUP PR 180 mg (fasted)
NB-233	Assess the effects of glyburide or food on the plasma PK of NB 8/90 tablets in healthy adults. Open-Label Crossover	NAL PR 16 mg + BUP PR 180 mg Glyburide 6 mg (fed and fasted)
NB-236	Assess the effects of NB 8/90 tablets on the single-dose plasma PK of metoprolol in healthy adults genotyped as extensive metabolisers of CYP2D6. Open-Label, Steady-State, Crossover (extension)	Metoprolol IR 50 mg NAL PR 32 mg + BUP PR 360 mg + Metoprolol IR 50 mg (fed and fasted)
NB-237	Assess the relative BA of three different NAL PR/BUP PR combination tablets to NB 8/90 monolayer tablets in healthy adults. Open-Label, Single-Dose, Crossover	NAL PR 16 mg + BUP PR 180 mg (fasted)
NB-238	Assess the relative BA of two NAL PR/BUP PR combination tablets to NB 8/90 monolayer	NAL PR 16 mg + BUP PR 180 mg (fasted)

	tablets in healthy adults. Open-Label, Crossover	
NB-239	Assess the relative BA of a combination monolayer tablet to NB 8/90 tablets after a moderate-fat meal. Open-Label, Crossover	NAL PR 16 mg + BUP PR 180 mg (fed)

Clinical pharmacology studies

Study	Primary Objective	Secondary Objective(s)	Doses/Regimen	Formulation
IR-PET	Brain receptor occupancy	Correlation of plasma exposure to receptor occupancy	8, 16 and 24 mg Nal BID	IR- commercial tablets compounded into lower dose capsules
NB-222	Brain receptor occupancy for PR formulation	Correlation of plasma exposure to receptor occupancy	10 and 25 mg Nal BID	PR- 5 mg Nal minitabs
NB-232	PK interaction with atorvastatin (80 mg) and valsartan (320 mg)	Relative BA of two strengths of trilayer tablet	8 mg Nal/180 mg Bup 16 mg Nal/180 mg Bup ± 80 mg atorvastatin or 320 mg valsartan Single Dose	PR - NB 4/90 or 8/90 tablets
NB-233	Determine the effect of food on Nal and Bup exposure	PK interaction with glyburide	16 mg Nal/180 mg Bup ± 6 mg glyburide Single Dose	
NB-234	PK interaction with nifedipine and lisinopril	None.	16 mg Nal/180 mg Bup ± 90 mg nifedipine ER or 40 mg lisinopril Single Dose	
NB-236	PK interaction with metoprolol	Assess PK effect of food Assess multiple-dose PK	8 mg Nal/90 mg Bup single dose or 16 mg Nal/180 mg Bup multiple dose ± 50 mg metoprolol	

Phase 2 and 3 studies

Study ID	Phase	No. of Study Centres Location	Study Design	Test Product and Dose	# Subjects Randomised/ Completed	Treatment Duration	Age*, Sex	Study Population	Primary Endpoints
NB-301	3	34 US	Multicentre, randomised, double-blind, placebo-controlled study	Placebo Naltrexone PR 16 mg/day and Bupropion PR 360 mg/day (NB16) Naltrexone PR 32 mg/day and Bupropion PR 360 mg/day (NB32)	Placebo: 581/290 NB16: 578/284 NB32: 583/296	56 week double-blind (and a 2 week double-blind discontinuation assessment during Weeks 57-58)	18 to 66 years, male and female	Obese subjects with or without controlled hypertension and/or dyslipidaemia	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline
NB-302	3	9 US	Multicentre, randomised, double-blind, placebo-controlled study	Placebo Naltrexone PR 32 mg/day and Bupropion PR 360 mg/day (NB32)	Placebo: 202/118 NB32: 591/342	56 week double-blind	19 to 65 years, male and female	Obese subjects with or without controlled hypertension and/or dyslipidaemia; nonsmokers; participated in intense group lifestyle modification counseling (28 sessions)	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline

Study ID	Phase	No. of Study Centres Location	Study Design	Test Product and Dose	# Subjects Randomised/ Completed	Treatment Duration	Age*, Sex	Study Population	Primary Endpoints
NB-303	3	36 US	Multicentre, randomised, double-blind, placebo-controlled study	Placebo Naltrexone PR 32 mg/day and Bupropion PR 360 mg/day (NB32) From Week 28 through Week 44, non-responders on NB32 were re-randomised to either NB32 or Naltrexone PR 48 mg/day and Bupropion PR 360 mg/day (NB48)	Placebo: 495/267 NB32: 1001/538 Re-randomised to NB48: 123	56 week double-blind	18 to 65 years, male and female	Obese subjects with or without controlled hypertension and/or dyslipidaemia	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline Primary efficacy evaluation was conducted at Week 28 with secondary evaluation at Week 56
NB-304	3	53 US	Multicentre, randomised, double-blind, placebo-controlled study	Placebo Naltrexone PR 32 mg/day and Bupropion PR 360 mg/day (NB32)	Placebo: 170/100 NB32: 335/175	56 week double-blind	20 to72 years, male and female	Obese subjects with type 2 diabetes and with or without controlled hypertension and/or dyslipidaemia	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline

Study ID	Phase	No. of Study Centres Location	Study Design	Test Product and Dose	# Subjects Randomised / Completed	Treatment Duration	Age*, Sex	Study Population	Primary Endpoints
NB-201	2	7 US	Multicentre, randomised, double-blind, placebo- and monotherapy -controlled study	Placebo** Naltrexone 48 mg/day** (Nal48) Bupropion PR 400 mg/day (B400) Naltrexone 16 mg/day and Bupropion PR 400 mg/day (Nal16/B400) Naltrexone 32 mg/day and Bupropion PR 400 mg/day (Nal32/B400) Naltrexone 48 mg/day and Bupropion PR 400 mg/day (Nal48/B400)	Placebo: 88/69 Nal48: 61/37 B400: 66/45 Nal16/B400: 67/41 Nal32/B400: 70/52 Nal48/B400: 67/36 Crossover: Placebo to Nal32/B400: 61/50 Nal48 to Nal32/B400: 34/34	24 week double-blind, followed by 24 week extension	18 to 60 years, male and female	Obese subjects without complicated obesity who are nonsmokers	Percent change from baseline to endpoint in body weight
OT-101	POC	8 US	Multicentre, randomised, single-blind placebo- and monotherapy study	Placebo** Naltrexone 50 mg/day** (Nal50) Bupropion PR 300 mg/day (B300) Naltrexone 50 mg/day and Bupropion PR 300 mg/day (Nal50/B300)	Placebo: 59/38 Nal50: 60/41 B300: 59/47 Nal50/B300: 60/37 Crossover: Placebo to Nal50/B300: 18/15 Nal50 to Nal50/B300: 16/12	16 week, followed by up to 32 week extension	18 to 60 years, male and female	Obese subjects without complicated obesity who are nonsmokers	Percent and absolute change from baseline to endpoint in body weight

Study ID	Phase	No. of Study Centres Location	Study Design	Test Product and Dose	# Subjects Randomised/ Completed	Treatment Duration	Age*, Sex	Study Population	Primary Endpoints
NB-301 Sub-study	3	8 US	Multicentre, randomised, double-blind, placebo-controlled study	Placebo Naltrexone PR 16 mg/day and Bupropion PR 360 mg/day (NB16) Naltrexone PR 32 mg/day and Bupropion PR 360 mg/day (NB32)	Placebo: 77 45 with DEXA 24 with CT scan NB16 and 32: 137 79 with DEXA 34 with CT scan	52 week double-blind assessment	18 to 65 years, male and female	Obese subjects with or without controlled hypertension and/or dyslipidaemia	Change from baseline in total fat mass

*Age ranges provided here reflect the actual age ranges enrolled in each study.

** The subjects in these treatment groups crossed over to combination treatment during the extension phase.

The analytical methods used for the drug analyses, the pharmacokinetic data analyses and the applied statistical methods are generally considered to be sufficient and justifiable.

2.4.2. Pharmacokinetics

- Absorption

Following single oral administration to healthy subjects of the NB formulation intended to be marketed, Tmax of naltrexone and bupropion was approximately 2 and 3 hours, respectively.
The Tmax and Cmax values reflected the prolonged release properties of the formulation.

A different formulation was used in Phase 2 compared to Phase 3, both with regard to release properties (Immediate Release naltrexone versus Prolonged Release naltrexone) and strength (bupropion). Consequently, there is no bioequivalence link between Phase 2 and 3. However, none of the Phase 2 studies can be considered to be pivotal.

The Applicant has provided upon request a discussion on the impact of the formulation on the stereoselective metabolism of bupropion. It is accepted that a change in the absorption rate could potentially alter the exposure of the different enantiomers of bupropion and it metabolites. However, historical information shows that the release rate has minimal impact on the bioavailability, which would not be expected if there was a significant change in the ratio of the two enantiomers. Thus, it is not considered that chiral assays are required.

The formulations for the Phase 3 studies were produced by different manufacturers at different sites. Full bioequivalence links have not been established between all the formulations used in Phase III and the formulation intended for the market. The Applicant was asked to provide more information about the extent of the use of the non-bioequivalent tablets and discuss the implications for the results of the Phase 3 studies where they have been used. The requested information has now been provided, and it is concluded that the results of studies NB-302 and NB-304 (where not all the formulations used was bioequivalent with the commercial formulation) are not biased in favour of NB due to differences in formulations. Further, the efficacy results are further substantiated by studies NB-301 and NB-303 where the commercial formulation was used exclusively.

Food effect

The combined results of the studies investigating food interactions showed a quite pronounced effect of food, in particular in terms of naltrexone exposure. The food effect appeared to be somewhat more pronounced with high-fat meals and to diminish with multiple dosing. In the Phase 3 studies, patients were advised to take the study medication with food. Therefore, it is likely that the safety (and efficacy) implications of the food effect are captured to a large extent in these studies.

The section 4.2 in the SmPC is considered adequate as it is stated that NB should preferably be taken with food. This is supported since patients were advised to take NB with food in the Phase 3 studies (although not in the ongoing NB-CVOT study).

Metabolism

Naltrexone is mainly metabolized to the active metabolite 6β-naltrexol by dihydrodiol dehydrogenases (DD1, DD2 and DD4). Other major metabolic routes are the formation of the metabolites 2-hydroxy-3-O-methyl naltrexone and 2-hydroxy-3-Omethyl-6β-naltrexol, believed to be mediated by catechol-O-methyl transferases (COMT), and glucuronidation, thought to be mediated by UGT1A1 and UGT2B.

The potency of 6β-naltrexol is generally considered less than that of naltrexone, but is thought to contribute to efficacy because it reaches higher concentrations in plasma than naltrexone. Following single doses of NB tablets, the terminal elimination half-life of naltrexone was approximately 5 hours.

Following single doses of NB tablets, the terminal elimination half-life of bupropion was approximately 21 hours. However, the pharmacologically active metabolites have considerably longer half-lives.

Bupropion is extensively metabolized in humans. There are 3 major active circulating metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion. Following single dose, total systemic exposure (AUC) of hydroxybupropion was approximately 12-fold that of the parent drug, threohydrobupropion and erythrohydrobupropion were approximately 4.5- and 0.8-fold that of the parent drug.

The enzymatic reactions responsible for bupropion metabolism are not completely understood. CYP2B6 is known to be mainly responsible for oxidation of bupropion to hydroxybupropion in humans. Published data indicate that 11β-Hydroxysteroid Dehydrogenase 1 is the major enzyme responsible for threohydrobupropion formation. The metabolic pathway responsible for the formation of erythrohydrobupropion metabolite is unknown. In addition the metabolic pathway leading to the formation of the m-Chlorohippuric acid metabolite is also unknown. However, it likely involves non-CYP450 metabolic isozymes.

Elimination

In humans naltrexone and its metabolic products are primarily excreted in urine. After oral administration, approximately 37 to 60% of the total dose is excreted in urine within 48 to 72 hrs, mainly as conjugated and unconjugated forms of naltrexone and 6β-naltrexol.

The major elimination pathway of bupropion appears to be oxidation of the bupropion side chain which results in the formation of a glycine conjugate of m-chlorobenzoic acid, which is then excreted as the major urinary metabolite.

Bupropion metabolites are predominantly excreted in urine (87%) with a lesser amount in faeces (10%).

Upon request, the Applicant provided an detailed overview of the metabolite profile and excretion pathways of bupropion and naltrexone. The SmPC summarise the elimination pathways and provides a warning that inhibitors or inducers of UGT 1A2 and 2B7 may alter the exposure of naltrexone.

Genetic polymorphism

Genetic polymorphism appear not be relevant for the pharmacokinetics of naltrexone and 6β-naltrexol.

One particular genotype (CYP2B6*4 variant) is not uncommon and appear to be associated with an increased biotransformation of bupropion to hydroxybupropion. Since both the parent compound and the metabolite are pharmacologically active, the clinical implications are difficult to judge. The Applicant provided an adequate discussion on the possible effect of the CYP2B6*4 variant on bupropion and hydroxybupropion concentrations as well as possible clinical consequences, if any. The frequency of the allele is not trivial, but based on the overall efficacy, safety and tolerability profile of NB, it appears excessive to require CYP2B6 genotyping in relation to NB therapy.

Dose proportionality, steady state exposure and PK variability

Very limited investigations of dose proportionality for naltrexone did not reveal indications of significant deviations from dose proportionality in the 8-16 mg range. The Applicant has presented further analyses for Cmax which appears to show linearity across the dose range of 8 to 200 mg. This is considered reassuring.

The Applicant was requested also to further discuss the steady state exposure of bupropion and its major metabolites with NB when compared to bupropion in other indications. The provided data suggested that the steady state exposure of bupropion and metabolites with NB at maintenance dose is higher than with bupropion when administered as mono-component used for depression and as smoking cessation agent. This was considered acceptable since adverse events associated with bupropion, in particular seizures, appeared not to be more frequent with NB than with bupropion in its licensed indications.

The between subjects pharmacokinetic variability for naltrexone is quite pronounced with %CV values often exceeding 60% for Cmax and AUC.

The within-subject variability for Cmax and AUC is moderate for both naltrexone and bupropion, with %CV values in the range of approximately 10-16%.

Naltrexone exposure was somewhat lower in obese subjects compared to non-obese subjects. However, given the high between subjects variability, there was a huge overlap between the two groups.

Special populations

The PK data in special populations generated with NB as well as the individual components are relatively scarce - despite the fact that naltrexone and bupropion have been marketed for many years as individual medicines.

- Renal impairment

There is no experience with NB in renal impairment in the Phase 3 programme, although there is some experience in the ongoing CVOT study. Limited experience with each individual component indicates marked increases in exposure of both naltrexone and bupropion in moderate renal impairment. The Applicant initially proposed a SmPC which recommended a reduced frequency and/or dose for consideration in patients with renal impairment (except end-stage renal impairment where a contraindication was proposed). However, there are no clinical data to support a lower dose or a reduced frequency of NB in weight management. Upon discussion during the procedure, the Applicant has agreed that the SmPC should state that NB is contraindicated in severe renal impairment and not recommended in patients with moderate renal impairment. This is supported by the CHMP .

For both NB-treated and placebo-treated patients, the frequency of serious adverse events and adverse events leading to study drug discontinuation increased with decreasing renal function. Further, for some adverse events (gastrointestinal in particular), the increase with decreasing renal function was higher in NB-treated patients than in the placebo group. Even though the placebo-subtracted incidence of some adverse events was higher even in mild renal impairment than in patients with normal renal function, the difference to patients with intact renal function is not considered to be of a magnitude that warrants a non-recommendation for patients with mild renal impairment. In these patients, the SmPC recommends no need for drug adjustment but assessment of eGFR should be performed prior to initiating therapy in patients at elevated risk for renal impairment (in particular patients with diabetes or elderly).

- Hepatic impairment

There is no experience with NB in hepatic impairment. Studies in severe hepatic impairment with each individual component show multi-fold increases in exposure of both naltrexone and bupropion. This justifies the proposed contraindication in severe hepatic impairment. There is apparently very little information on oral naltrexone in mild and moderate hepatic impairment. Mild or moderate hepatic impairment seems to increase the exposure of bupropion and hydroxybupropion and to increase the PK variability.

The SmPC states that NB is not recommended in patients with mild or moderate hepatic impairment.

The clinical feasibility of restricting use to patients with normal liver function, and no worse than mild kidney function in the co-morbid obese population was discussed with the applicant.

In addition, the use of NB in renally and hepatically impaired patients will be addressed in the post-authorisation setting in multiple dose PK studies in patients with hepatic and renal impairment.

- Gender

Exposure to both naltrexone and bupropion appears to be moderately higher in females than in males.

- Race

The data on the effect of race indicating only small effects are limited by the fact that only Caucasian and Black subjects contributed significantly with PK data.

- Elderly

Pharmacokinetic data with NB in elderly is very limited. There is also limited PK data in elderly with the individual components. Historical data suggest a modest effect of age on the PK of naltrexone and moderately reduced bupropion clearance in elderly and increased accumulation of bupropion and metabolites. The Applicant proposed to introduce a cautionary statement for patients over 65 years and a non-recommendation for patients over 75 years in section 4.2 of the SmPC. This is supported.

- Children

There is apparently no PK data available on naltrexone in children and only limited experience with bupropion. NB is only proposed for use in adults. A statement is introduced in the SmPC about the efficacy and safety not being established in children and adolescents above 18.

Drug drug interactions

Overall, the in vitro and in vivo programme performed to address drug-drug interactions is acceptable.

The Applicant was asked to further address the time dependency of naltrexone inhibition of CYP2C19. While there was a slight increase in the degree of inhibition of CYP2C19 by naltrexone following a

pre-incubation, the fact that this inhibition was observed only at the highest dose tested and was relatively modest means that this inhibition is unlikely to be clinically relevant.

A discussion of the effect of bupropion on metformin exposure was also requested. Analyses from the clinical studies NB-CVOT and NB-304 did not indicate an increased metformin exposure when metformin was administered with NB, judged by the lack of lactate acidosis and hypoglycaemia events in the clinical studies.

A number of clinical DDI studies have been undertaken by the Applicant.

There are no suggestions of any PK interaction between naltrexone and bupropion. A number of clinically relevant PK interactions with NB have been identified. They have now been well reflected in the SmPC.

In conclusion, the pharmacokinetic evaluation of NB is considered acceptable.

2.4.3. Pharmacodynamics

Naltrexone is a specific, long-acting competitive antagonist at opioid receptors. Its primary metabolite, 6β-naltrexol, has similar pharmacological activity, although with a lower potency.

Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine). Bupropion has three basic metabolites, hydroxybupropion, threohydrobupropion and erythrohydrobupropion, which also exhibit pharmacological activity.

The proposed mechanism of action in management of weight is considered plausible.

Two PET studies investigated opioid receptor occupancy with naltrexone to support the investigated naltrexone doses as part of the NB fixed dose combination in the NB-201 Phase 2 study. An fMRI study provided supportive evidence for pursuing development of NB in management of weight.

The dose-response investigations with regard to naltrexone are based on both pharmacodynamic studies and a larger-scale Phase 2 study of longer duration with clinical endpoints. The selection of naltrexone doses for the confirmatory studies anchored around the NB32 dose but also investigating NB16 and to some extent NB48 is supported.

The Applicant has also justified the dose of 360 mg for bupropion.

The CHMP originally considered that the proposed fixed dose combination had not been adequately investigated in terms of superiority over the mono components and asked the Applicant to provide further justification. This issue was raised due to a concern that the therapeutic contribution of each individual component at the exact dose used in the combination was not clearly shown relative to the combination. The Applicant has justified this by reiterating the rationale for the combination, reviewing the results of study NB201, and by detailing the PK and PD data used to bridge the Phase 2 dose combinations to the doses and formulations used in Phase 3.

There is no non-clinical signal suggesting a potential for QTc prolongation. Neither bupropion nor naltrexone has historically been associated with prolongation of QTc interval. The clinical studies conducted with NB do not indicate that NB causes QTc increases. Hence, the omission of a thorough QTc study is considered acceptable.

In the PK/PD analyses, weight loss was shown to occur across a wide range of naltrexone and bupropion exposure levels. For some efficacy endpoints, improvements tended to be greater with increasing exposure. No exposure-response relationship was shown for any of the investigated safety and tolerability parameters.

Given the reports of neuropsychiatric events with bupropion and alcohol, it is appropriate to recommend that intake of alcohol should be limited or avoided during treatment with NB. This is in line with the recommendations given in the bupropion SmPC. Thus, the proposed recommendation that consumption of alcohol should be minimised or avoided is supported.

Considering the mechanism of action for bupropion, further discussion about potential pharmacodynamic interactions with serotonergic agents (also including other drug classes than SSRIs and TCAs, e.g. SNRIs) was requested. Based on adverse events data presented by the Applicant, it is concluded that there is no firm evidence to indicate pharmacodynamic interactions between NB and SSRI/SNRIs. MAO inhibitors are contraindicated due to their propensity to enhance the catecholaminergic pathways.

The influence of A118G polymorphism was not investigated in the NB weight management programme. It cannot be excluded that it may be of significance and could explain some of the variability in the response to NB. However, it is likely to be only one of several intrinsic and extrinsic factors, which contribute to the weight loss associated with NB. No specific precautions are deemed necessary with regard to A118G polymorphism.

In conclusion, the pharmacodynamic evaluation of NB is considered acceptable.

2.4.4. Discussion on clinical pharmacology

The Applicant was requested to explain the rationale for the development of a prolonged release formulation of naltrexone. The Applicant demonstrated that the receptor occupancy of naltrexone is not higher following similar doses of immediate release compared to controlled release. Therefore, the lower Cmax does not appear to impact on the degree of receptor occupancy and therefore efficacy. This explanation is considered acceptable by the CHMP.

A large part of the clinical pharmacology documentation is based on historical data on the already marketed individual monocomponents.

The pharmacodynamics and phamacokinetics of NB have been sufficiently investigated by the Applicant. The pharmacokinetics of NB in patients with renal and hepatic impairment has not yet been fully investigated, but this will be addressed in the post-marketing setting, and the current warnings and contraindications in the label are acceptable. All questions raised during the assessment have been sufficiently addressed and reflected in the proposed post-authorisation studies included in the RMP (multiple dose PK studies in patients with hepatic and renal impairment).

2.4.5. Conclusions on clinical pharmacology

No major objections have been identified with respect to the clinical pharmacology programme, and other concerns have been resolved.

2.5. Clinical efficacy

The Applicant states that all trials have been conducted in compliance with GCP. No observations have been made during the assessment of the dossier indicating significant GCP non-compliance.

2.5.1. Dose response studies

- ✓ Study OT-101

Study OT-101 was a Phase 2 multicentre, randomised, placebo-controlled and monotherapy (naltrexone 50 mg and bupropin 300 mg) controlled proof of concept study to assess the safety and efficacy of combination therapy (immediate release naltrexone 50 mg daily and bupropion PR 300 mg daily) in subjects with uncomplicated obesity. The treatment period was 16 weeks and there was an optional 32 week extension period. For the extension period, subjects on placebo or naltrexone (N) 50 mg alone were placed on open-label therapy with naltrexone 50 mg/bupropion PR 150 mg BID (N50/B300).

Study OT-101 evaluated the efficacy and safety of the combination treatment with bupropion and naltrexone compared to the mono-components alone and placebo. It is assumed that the combination therapy should be more efficacious than the monotherapy, i.e. Nal50/B300 should be better than Nal50 and B300 alone. This was however not the case in Study OT-101 as bupropion 300 mg alone was not statistically significant different from Nal50/B300 for the LS mean percent change in total body weight at week 16 LOCF and the study was stopped early around the 24-week assessment.

The LS mean percent change in total body weight from baseline to Week 16 LOCF was -4.0% in the N50/B300 group. The LS mean percent change in total body weight from baseline to Week 16 LOCF in the other three treatment groups, and the p-values for their contrast of the weight loss compared with the N50/B300 group, were as follows: B300: -3.6% (p=0.274); N50: -2.0% (p=0.005); and placebo: -1.0% (p <0.001).

The analyses of the completers analysis set differed from the analyses in the full analysis set principally by the larger adjusted LS mean percent change in total body weight from baseline to Week 16 for the treatment group N50/B300 (-4.8%).

A completer's analysis suggested a greater weight loss in the combination group compared to the monotherapies and placebo when treated for longer time.

- ✓ *Study NB-201*

Study NB-201 was a Phase 2 multicentre, randomised, double-blind, placebo- and monotherapy-controlled study with a treatment period of 24 weeks (primary) and an extension period of 24 weeks. Subjects were non smoking with uncomplicated obesity (BMI ≥ 30 and ≤40) and enrolled in two cohorts. Cohort 1 included 5 groups: placebo, N48, B400, N16/B400, and N48/B400. Cohort 2 consisted of two groups: placebo and N32/B400. Subjects were only randomised into Cohort 2 after each site's enrollment in Cohort 1 was completed. The statistical analysis plan was amended, prior to unblinding of either cohort, to permit an integrated dose-response assessment of the combination naltrexone doses studied across cohorts.

After Week 24, subjects in the placebo and immediate release naltrexone 48 mg monotherapy groups who chose to continue study participation in the 24 week open-label extension were crossed over to receive treatment with immediate release naltrexone 32 mg administered with bupropion PR 400 mg (N32/B400). The primary endpoint for the study was assessed at Week 24.

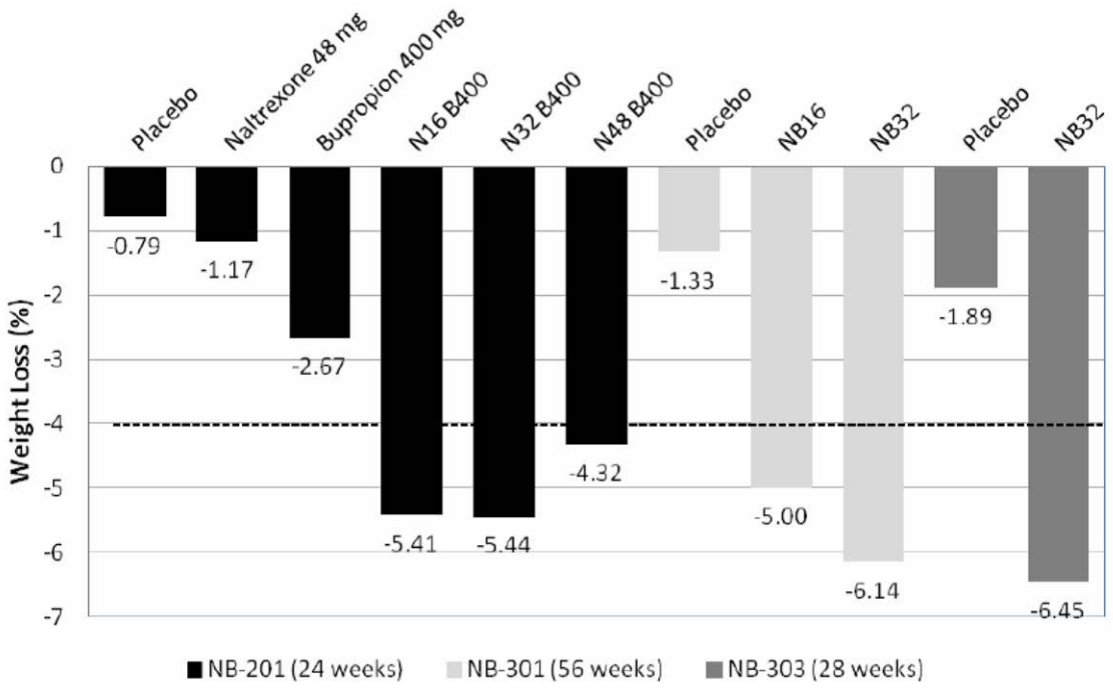
With both the doses of N16/B400 and N32/B400, the weight loss after 24 weeks was statistically significantly different compared to placebo, N48 and B400 alone. However, this was not the case with the higher dose of N48/B400, which was not statistically significant better than placebo and the 2 mono-components. The mean weight loss is presented in Figure 2.7.3-3.

Table 2.7.3-33 Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Week 24 Endpoint in Study NB-201 (Intent to Treat Population)

Statistic	Placebo (n=84)	Naltrexone 48 (n=49)	Bupropion PR 400 mg (n=57)	Nal16/B400 (n=54)	Nal32/B400 (n=63)	Nal48/B400 (n=54)
No. (%) with ≥ % decrease	13 (15%)	5 (10%)	15 (26%)	28 (52%)	32 (51%)	21 (39%)
95% CI	8%, 23%	2%, 19%	15%, 38%	39%, 65%	38%, 63%	26%, 52%
p-value vs. Placebo	--	--	--	< 0.0001	< 0.0001	0.0018
p-value vs. Naltrexone 48	--	--	--	< 0.0001	< 0.0001	0.0008
p-value vs. Bupropion PR 400	--	--	--	0.0058	0.0061	0.1573

Source: NB-201 CSR Table 5.2.1.1c and Figure 11-3
Nal16/B400 = naltrexone 16 mg / bupropion PR 400 mg
Nal32/B400 = naltrexone 32 mg / bupropion PR 400 mg
Nal48/B400 = naltrexone 48 mg / bupropion PR 400 mg
ITT population comprised all randomised subjects who had at least one postbaseline measurement of body weight. Pairwise comparisons using Chi-square test.

Figure 2.7.3-3 Body Weight (kg), Percent Change from Baseline to Endpoint (Studies NB-201, NB-301, and NB-303)



Source: CSR NB-201 Table 5.1.1.c, ISE Table ISE.301.1-6 and Table ISE.303.1-6A
Endpoint was Week 24 for Study NB-201 and Week 56 for NB-301 and Week 28 for NB-303. NB-201 results are for the intent-to-treat analysis set; NB-301 and NB-303 results are for the full analysis set.
Note: the dashed line indicates the hypothetical additive weight loss (~4%) with naltrexone 48 mg and bupropion PR 400 mg based on simple summation of weight loss observed with the individual drugs in Study NB201.

The dose-finding study NB-201 showed that the two doses N16/B400 and N32/B400 yielded similar weight losses at 24 weeks in uncomplicated obesity patients.

The dose selection was also based on three published randomised controlled trials with bupropion PR in patients with obesity demonstrating greater weight loss than placebo, and that doses of 300 mg/day or 400 mg/day of bupropion PR were well tolerated (Gadde 2001; Anderson 2002; Jain 2002). Three published randomised controlled trials with naltrexone in patients with obesity, however, did not demonstrate clinically significant weight loss (Atkinson 1985; Malcolm 1985; Mitchell 1987).

N16/B360 was evaluated also in study NB-301 and N48/B360 in study NB-303. In the description of the Phase 3 studies, these doses are referred to as NB32, NB16 and NB48, respectively.

CHMP comments

Considering the results of Study NB-201, it is agreed that there is a rationale for combination therapy with naltrexone and bupropion since the combinations N16B400 and N32B400 showed superior efficacy over each of the individual components N48 and B400.

It is considered acceptable that the tablet formulation and doses used in Study NB-201 are not identical to the ones used in the Phase 3 programme.

The Applicant chose to proceed with the intermediate dose N32/B360 for the Phase 3 trials which is also the recommended dose.

The dose-response investigations with regard to naltrexone and the naltrexone doses carried into the Phase 3 programme are supported. It is also supported that daily bupropion doses higher than 400 mg was not investigated given the risk of seizures.

2.5.1. Main studies

The applicant submitted four pivotal studies NB-302, NB-302, NB-303, and NB-304 supporting the indication in weight management.

2.5.1.1. General features

For practical reasons, some common features regarding design, efficacy endpoints and statistical analyses for the rather similar pivotal trials will be discussed in this introduction. Subsequently, each study will be presented individually. The Quality of Life results will be reviewed jointly after the presentation and review of the individual studies.

Methods and Study Participants

The NB Phase 3 programme included four pivotal, multicentre, randomised, double-blind, placebo-controlled studies (Study NB-301; Study NB-302; Study NB-303; and Study NB-304). Across these studies, the efficacy, safety and tolerability of NB were evaluated in obese and overweight subjects receiving customary diet and behavioural counselling, including prescribed exercise (Studies NB-301 and NB-303) and in obese/overweight subjects undergoing intensive lifestyle modification counselling (Study NB-302).

One study was conducted in obese/overweight subjects with type 2 diabetes (Study NB-304).

Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI ≥30 and ≤45 kg/m^2 for subjects with uncomplicated obesity and with a BMI of ≥27 and ≤45 kg/m^2 for overweight or obese subjects with controlled hypertension and/or dyslipidaemia.

One of the four pivotal studies (Study NB-301) included a sub-study in which subjects underwent body composition analysis and visceral fat measurement at baseline and after approximately

52 weeks of therapy, while another (Study NB-303) included a sub-study in which blood pressure was measured over a 24-hour period at baseline, and after approximately 24 and 52 weeks of therapy.

Treatments

All four studies investigated a daily dose of naltrexone 32 mg PR combined with bupropion 360 mg PR (NB32).

Studies NB-301 and NB-303 also investigated other doses of naltrexone, while the dose of the bupropion components remained the same.

Study NB-301 investigated two different doses of naltrexone PR, namely 16 mg and 32 mg, combined with bupropion 360 mg PR, and in study NB-303 NB32 subjects could be re-randomised at the beginning of Week 28 through Week 44, to receive naltrexone PR 48 mg combined with bupropion 360 mg PR.

The ancillary therapy consisted of diet instruction, behaviour modification advice and physical activity suggestions. The hypocaloric diet of a deficit of 500 kcal/ day based on the WHO algorithm for calculation of resting metabolic was outlined. Furthermore, a prescription for walking at least 30 minutes three times (study NB-303 and NB-304) or most days of the week study NB-301). In Study NB-302, a more intensive behaviour modification programme was prescribed including more physical exercise.

Outcomes/endpoints

Treatment effects were evaluated using a two-sided significance level of 0.05. The primary efficacy endpoints were (1) percent change from baseline to endpoint in body weight and (2) the proportion of subjects achieving ≥ 5% weight loss at endpoint.

In all studies except Study NB-303, the primary endpoint was assessed at Week 56. In Study NB-303, data were analysed at the Week 28 primary endpoint (prior to re-randomisation), analyses of weight loss at Week 56 were a secondary endpoint.

In the NB-303 study, subjects on NB32 who had not achieved at least a 5% decrease from baseline in body weight at Week 28 were re-randomised to either continue on NB32 or to receive a higher dose NB48. Subjects on NB32 not previously re-randomised who did not maintain at least 5% of baseline body weight during Weeks 32-44 were also re-randomised at those visits. Subjects were only re-randomised once

Efficacy endpoints

All four studies employed the FDA recommended primary endpoints of mean and categorical changes from baseline in body weight following 1 year of treatment, as well as various pre-specified secondary endpoints such as the proportion of subjects who achieved ≥ 10% decrease from baseline in body weight and changes in waist circumference and lipids. Per FDA Guidance, efficacy can be demonstrated by achieving one of the two primary endpoints.

Based on CHMP recommendations (CHMP/EWP/281/96/Rev. 1), the primary demonstration of efficacy should be based on the difference in mean weight loss from baseline in the active treatment group of at least 10%, and also at least 5% greater than that seen with placebo. The guideline also indicates that an alternative means of demonstrating efficacy could be based on having a significantly greater proportion of subjects who lose more than 10% of their baseline body weight in the active treatment group compared with placebo.

The following FDA-recommended primary efficacy endpoints were employed for the four Phase 3 studies:

- The percent change from baseline in body weight at Week 56 (Last Observation Carried Forward [LOCF]) for Studies NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for Study NB-303.
- The proportion of subjects who achieved ≥ 5% decrease from baseline body weight at Week 56 (LOCF) for studies NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for study NB-303.

Secondary endpoints included the following:

- The percent change from baseline in body weight (LOCF) and the proportion of subjects who achieved >5% decrease from baseline body weight at Week 56 (LOCF) for study NB-303.
- The proportion of subjects who achieved ≥ 10% decrease from baseline in body weight.
- Waist circumference change from baseline to endpoint.
- Lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides) change from baseline to endpoint.
- Glucose and insulin parameters change from baseline to endpoint.
- Glycaemic control (NB-304 only) – as measured by percent change from baseline in haemoglobin A1c (HbA1c) and proportion of subjects with HbA1c <6.5%, with HbA1c <7.0%, needing rescue medications, needing change in doses of oral hypoglycaemic agents, and discontinued due to poor glycaemia control.
- High-sensitivity C reactive protein (hs-CRP) change from baseline to endpoint.
- Systolic and diastolic blood pressure.
- Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire
- Control of Eating (COE) questionnaire for studies NB-301, NB-303 and NB-304, Item 19 on the COE questionnaire was pre-specified and included as a secondary endpoint. This item asked "Generally, how difficult has it been to control your eating?"
- Food Craving Inventory (FCI) questionnaire.
- Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) questionnaire.

Statistical methods

Unless otherwise specified, efficacy analyses were conducted on the full analysis set or the completers analysis set. The full analysis set (a modification of the intent-to-treat principle) included all randomised subjects who had a baseline weight measurement and at least one post-baseline weight measurement while on study drug (i.e., active treatment or placebo). For Studies NB-301, NB-303, and NB-304, Week 56 completers included all randomised subjects who had a baseline weight measurement, a post-baseline weight measurement, and who completed 56 weeks of treatment. For Study NB-303, Week 28 Completers included all randomised subjects who had a baseline weight measurement, a post-baseline weight measurement and who completed 28 weeks of treatment. For Study NB 302, completers included all randomised subjects who had a baseline weight measurement and a post-baseline weight measurement at Week 56 while on study drug. In all summaries, subjects were grouped according to their randomised treatment group assignment. The analyses presented in this document focus on changes in efficacy measurements from baseline to endpoint.

Baseline was defined as the last non-missing measurement before, or at the time of, randomisation. Endpoint was defined as the last non-missing post-baseline weight measurement while on study drug (last observation carried forward [LOCF]). Efficacy assessments performed within 1 day after the last dose date were considered valid.

Each study was designed to control for multiplicity and maintain a 5% false positive rate for the hypothesis testing of the primary and secondary endpoints. The analysis of the secondary efficacy endpoints required both primary endpoints to be significant and was structured in a sequential, hierarchical manner referred to as a CTP. The sequential order differed slightly in each study protocol. Among other secondary endpoints, the analysis of the proportion of subjects with ≥ 10% decrease in total body weight from baseline (10% responders) was planned in the SAP of the four Phase 3 studies.

In general, continuous change from baseline to endpoint variables were analysed using an analysis of covariance (ANCOVA) model. Unless otherwise specified, the model contained the main effects of treatment and study centre with the baseline measurement as the covariate. Unless otherwise specified, categorical variables at endpoint were analysed using a linear logistic regression model, which included effects for treatment and study centre as the main effects, with baseline measurement as the covariate.

In addition to the completers analyses, other sensitivity analyses were conducted in the following analysis sets:

- the full analysis set using a repeated measures mixed effects model;
- the ITT analysis set using the last available data in the double-blind treatment phase and using a repeated measures mixed effects model; the ITT analysis set included all subjects who were randomised, had a baseline weight measurement and had at least one post-baseline weight measurement during the defined treatment phase, irrespective of being on study drug at the time of the post-baseline measurement;
- the all randomised analysis set subjects imputing the baseline value for subjects who discontinued prior to Week 56 (BOCF) and weight regain imputation methods (Sacks 2009).

CHMP comments

Despite the fact that the responder criterion employed in the co-primary endpoint (≥ 5% decrease) is not concordant with the CHMP-recommended (≥10%), the ≥10% criterion is included as pre-specified secondary endpoint. This is acceptable to the CHMP.

The primary and secondary endpoints are considered adequate to evaluate the efficacy of a medicine in weight control.

The study designs are acceptable with regard to randomisation, blinding and treatment duration.

None of the pivotal studies include an active reference. Orlistat is the only weight control medicine widely available in the EU. This medicine is associated with very common adverse reactions of a distinct, gastrointestinal nature (such as flatus with discharge, faecal urgency and fatty oily stool) which makes it difficult to blind this medicine if included as an active reference. For this reason, the omission of an active reference is acceptable.

The primary analysis is based on the full analysis set (FAS) and using LOCF as imputation method for missing data. However, given the high drop-out rate (about half of the patients discontinued prematurely), the sensitivity analyses have an important role in substantiating the results of the primary analysis because drop-outs may well be different from completers in terms of efficacy.

The Applicant has conducted a large number of sensitivity analyses: Analyses of the ITT analysis set (slightly different from the FAS), the completers set and the per protocol set as wells as analysis of repeated measures mixed effects model for the continuous endpoint and an analysis using baseline observation carried forward (BOCF) as imputation method for missing data.

The sensitivity analyses are considered generally well suited as supplemental analysis in the perspective of the high drop-out rate. These sensitivity analyses were prospectively planned on the

primary efficacy endpoint. In addition, post-hoc sensitivity analyses of the 10% responders secondary endpoint have been performed.

Please refer to subsequent CHMP comments on the choice of analysis population and imputation method for missing data.

The four pivotal studies NB-302, NB-302, NB-303, and NB-304 are described separately below :

2.5.1.2. Description of each study

Tabulated summaries of efficacy are presented at the end the section for each study. These tables present the results using the FAS analysis set and LOCF as imputation method for missing data as defined by the study protocols (FAS/LOCF). However, the CHMP considered other data sets and imputation methods ((ITT/LOCF) and (Randomised Population/BOCF)) more appropriate, and this has been reflected in the SmPC. Hence, these summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk-assessment (see later sections).

2.5.1.2.1. Study NB-301

Study title

A Multicenter, Randomized, Double Blind, Placebo Controlled Study Comparing the Safety and Efficacy of Two Doses of Naltrexone Sustained Release (SR) / Bupropion Sustained Release (SR) and Placebo in Obese Subjects.

Methods

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of naltrexone SR 16 mg/bupropion SR 360 mg, naltrexone SR 32 mg/bupropion SR 360 mg (referred to as NB16 and NB32, respectively throughout this report), and matching placebo in three treatment groups treated for 56 weeks, followed by a 2-week drug discontinuation period. All subjects received ancillary therapy at baseline and at Weeks 12, 24, 36 and 48 consisting of diet instruction, advice on behaviour modification, and suggestions for exercise.

There were 4 periods: screening period (up to 4 weeks, at least 2 visits; this serves ad´s eligibility evaluation for recruitment); titration period (4 weeks, 1 visit); maintenance period (52 weeks, 14 visits); drug discontinuation period (2 weeks, 1 visit) with either tapered or sudden withdrawal of study medication.

- **Study participants**

Selection criteria defined an eligible population of men or women, aged 18 to 65 years, with *uncomplicated obesity* (BMI ≥ 30 and ≤ 45 kg/m2) or *subjects with controlled hypertension and/or dyslipidaemia* and with BMI ≥ 27 kg/m2 and ≤ 45 kg/m2, who were without serious medical or psychiatric illness. The subjects should be normotensive (systolic ≤ 140 mm Hg; diastolic ≤ 90 mm Hg). Anti-hypertensive medications are allowed with the exception of alpha-adrenergic blockers and clonidine.

Fasting glucose < 126 mg/dL on no hypoglycaemic agents were allowed, fasting triglycerides should be <400 mg/dL.

Initiation or discontinuation of tobacco products including inhaled tobacco, chewing tobacco or snuff was not allowed in the 3 months prior to randomization or planned during study participation.

Loss or gain of more than 4.0 kilograms within 3 months prior to randomization was prohibited.

CHMP comment

Compliance was only measured for study medication. The lack of check of compliance with the diet and exercise regimen is considered a weakness, but not considered to affect the overall interpretability of the results.

- **Objectives / endpoints / statistical methods**

Please see above in the general introduction to the main studies.

- **Sample size**

The total sample size to be randomized was approximately 1650 subjects with a 1:1:1 randomization allocation between combination treatment and placebo groups. This sample size provided 99% power to detect a statistically significant difference between placebo and the combination treatment arms for the co-primary efficacy endpoints. The power calculation was made assuming the mean weight loss from baseline to the Week 56 visit would be approximately 1% for subjects randomized to placebo and ≥ 6% for subjects randomized to either combination treatment arm. A common SD of 7% was assumed for all three groups, with the primary comparison between the placebo and each combination treatment arm made using a two-sample t-test and two-sided significance level of 5%.

A comparison was also explored between the two combination doses. It was assumed that a difference of approximately 1.1% (SD=7%) in the percentage change from baseline to Week 56 was to be observed. This assumed difference provided approximately 74% power to detect a statistically significant difference between the two combination doses. The study has 64% power to detect a statistically significant difference between treatment arms for the co-primary efficacy endpoint, weight decrease of ≥ 5% from baseline to Week 56. Using the same assumptions as stated above but allowing for 20% of randomized subjects not providing post-baseline data, the study has 99% power to detect a statistically significant difference between treatment arms for the co-primary efficacy endpoint, weight decrease of ≥ 5% from baseline.

- **Conduct of the study**

Some minor clarifications and adjustments were made, both in the protocol and in the statistical analysis plan, but are considered acceptable.

- **Results**

Number analysed

Table 6. Analysis Populations: All Randomized Subjects (Study NB-301)

Analysis Set	Placebo (N=581) n (%)	NB16 (N=578) n (%)	NB32 (N=583) n (%)	Total (N=1742) n (%)
Full Analysis Set	511 (88.0%)	471 (81.5%)	471 (80.8%)	1453 (83.4%)
Completers Analysis Set	290 (49.9%)	284 (49.1%)	296 (50.8%)	870 (49.9%)
Per Protocol Analysis Set	251 (43.2%)	263 (45.5%)	267 (45.8%)	781 (44.8%)
ITT (Intent-to-Treat) Analysis Set	536 (92.3%)	524 (90.7%)	538 (92.3%)	1598 (91.7%)
Safety Analysis Set: Double-Blind Treatment Phase	569 (97.9%)	569 (98.4%)	573 (98.3%)	1711 (98.2%)
Safety Analysis Set: Drug Discontinuation Phase	284 (48.9%)	283 (49.0%)	292 (50.1%)	859 (49.3%)

Data Source: Table 14.1-4. Abbreviations: NB16=naltrexone SR 16 mg/bupropion SR 360 mg; NB32=naltrexone SR 32 mg/bupropion SR 360 mg.
Full analysis set included all subjects who were randomized, had a baseline measurement, and had at least one post-baseline body weight measurement while on study drug.
Completers analysis set included all randomized subjects who had a baseline measurement, a post-baseline body measurement, and had completed 56 weeks of treatment.
Per-protocol analysis set included all full analysis subjects who received at least 28 weeks of study treatment and had been compliant with study drug (≥70% overall compliance).
ITT (Intent-to-Treat) analysis set included all randomized subjects who had a baseline body weight measurement, and had at least one post-baseline body weight measurement during the defined treatment phase.
Safety analysis set double-blind treatment phase included all randomized subjects who received at least one tablet of study drug and had at least one investigator contact/assessment at any time after the start of study drug, regardless of whether or not they discontinued the study.
Safety analysis set drug discontinuation phase included all randomized subjects who received at least one tablet of study drug and had completed the drug discontinuation phase.

Baseline data

Subjects in the full analysis set were a mean age of 44 years (range 18-66) and predominantly female (85.1%) with 75% in the White race subgroup and 19% in the Black or afican-american race subgroup; 13.1% were of Hispanic or Latino ethnicity. Subjects in the full analysis set had a mean weight of 99.8 kg and a mean BMI of 36.2 kg/m^2. There were 51% of subjects with dyslipidaemia, 27% with metabolic syndrome, 26% with impaired fasting glucose, and 22% with hypertension.

- **Outcomes**

The following tables summarise the primary efficacy results, i.e. the percent change in body weight from baseline to endpoint, and the proportion of subjects with body weight ≥5% Decrease from Baseline to Endpoint, and the proportion of subjects with bodyweight ≥10% decrease from baseline. Moreover, results of sensitivity testing are presented.

Table 2.7.3-1 Body Weight (kg), Percent Change from Baseline to Endpoint in Study NB-301 (Full Analysis Set)

Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
Baseline mean (SD)	99.29 (14.33)	100.11 (14.41)	100.17 (16.26)
% change from baseline, LSMean (SE)	-1.33 (0.30)	-5.00 (0.31)	-6.14 (0.31)
LS Mean difference from placebo (SE)	--	-3.67 (0.42)	-4.81 (0.42)
95% CI	--	(-4.50, -2.85)	(-5.63, -3.99)
p-value	--	< 0.001	< 0.001
LS Mean difference from NB16	--	--	-1.14
95% CI	--	--	(-1.98, -0.30)
p-value	--	--	0.008

Table 2.7.3-2 Sensitivity Analyses - Body Weight (kg), Least Squares Mean Percent Change from Baseline to Endpoint in Study NB-301

Sensitivity Analyses	Placebo (N=511)	NB16 (N=471)	NB32 (N=471)
ITT Analysis Set[a]	(n=536)	(n=524)	(n=538)
LS Mean Percent Change (SE)	-1.29 (0.29)	-4.48 (0.29)	-5.36 (0.29)
Diff of LS Mean Percent Change (95% CI)		-3.19 (-3.97, -2.41)	-4.07 (-4.85, -3.30)
p-value		<0.001	<0.001
Completers Analysis Set	(n=290)	(n=284)	(n=296)
LS Mean Percent Change (SE)	-1.83 (0.46)	-6.70 (0.46)	-8.07 (0.46)
Diff of LS Mean Percent Change (95% CI)		-4.87 (-6.09, -3.64)	-6.24 (-7.46, -5.03)
p-value		<0.001	<0.001
Per-Protocol Analysis Set[a]	(n=251)	(n=263)	(n=267)
LS Mean Percent Change (SE)	-2.34 (0.51)	-7.06 (0.49)	-8.29 (0.49)
Diff of LS Mean Percent Change (95% CI)		-4.73 (-6.05, -3.40)	-5.95 (-7.27, -4.63)
p-value		<0.001	<0.001

respectively, compared with placebo LS mean -1.83%, p<0.001.

Table 2.7.3-3 Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint in Study NB-301 (Full Analysis Set)

Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
No. (%) with ≥5% decrease	84 (16.44%)	186 (39.49%)	226 (47.98%)
95% CI	(13.22%, 19.65%)	(35.08%, 43.91%)	(43.47%, 52.49%)
Odds ratio vs. placebo	--	3.42	4.86
95% confidence limit for odds ratio	--	(2.52, 4.63)	(3.60, 6.57)
p-value	--	< 0.001	< 0.001
Odds ratio vs. NB16	--	--	1.42
95% confidence limit for odds ratio	--	--	(1.09, 1.85)
p-value	--	--	0.010

Table 2.7.3-4 Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint in Study NB-301

Sensitivity Analyses	Placebo n (%)	NB16 n (%)	NB32 n (%)
ITT Analysis Set[a]	N=536	N=524	N=538
Proportion with ≥5% Decrease in Weight	93 (17.35%)	190 (36.26%)	226 (42.01%)
Odds Ratio (95% CI)		2.75 (2.06, 3.67)	3.59 (2.69, 4.77)
p-value		<0.001	<0.001
Completers Analysis Set	N=290	N=284	N=296
Proportion with ≥5% Decrease in Weight	67 (23.10%)	155 (54.58%)	183 (61.82%)
Odds Ratio (95% CI)		4.20 (2.90, 6.08)	5.75 (3.97, 8.34)
p-value		<0.001	<0.001
Per-Protocol Analysis Set[a]	N=251	N=263	N=267
Proportion with ≥5% Decrease in Weight	67 (26.69%)	141 (53.61%)	162 (60.67%)
Odds Ratio (95% CI)		3.38 (2.31, 4.96)	4.62 (3.14, 6.80)
p-value		<0.001	<0.001

The CHMP primary endpoint, the proportion of Subjects with ≥10% Decrease from Baseline to Endpoint, is shown below:

Table 2.7.3-1 Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Endpoint in Study NB-301 (Full Analysis Set)

Statistic	Placebo (N=511)	NB16 (N=471)	NB32 (N=471)
n (%) with ≥10% decrease	38 (7.44%)	95 (20.17%)	116 (24.63%)
95% CI	(5.16%, 9.71%)	(16.55%, 23.79%)	(20.74%, 28.52%)
Odds ratio vs. placebo	--	3.21	4.19
95% confidence limit for odds ratio	--	(2.14, 4.81)	(2.82, 6.23)
p-value	--	< 0.001	< 0.001

Summary of efficacy for Study NB-301

This table presents the results using the FAS analysis set and LOCF as imputation method for missing data as defined by the study protocol (FAS/LOCF). However, the CHMP considered other data sets and imputation methods ((ITT/LOCF) and (Randomised Population/BOCF)) more appropriate, and this has been reflected in the SmPC.

Title: A Multicenter, Randomized, Double Blind, Placebo Controlled Study Comparing the Safety and Efficacy of Two Doses of Naltrexone Sustained Release (SR) / Bupropion Sustained Release (SR) and Placebo in Obese Subjects.			
Study identifier	NB-301		
Design	Randomized, Double-Blind, PBO-Controlled,		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	58 weeks: 4 weeks of titration; 52 weeks of treatment; 1 week of withdrawal; 1 week withdrawal without medication not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	NB 16 (naltrexone SR 16 mg/bupropion SR 360 mg)	Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). At the Week 56 visit subjects were re-randomized in a double-blind, 1:1 allocation ratio to undergo either tapered withdrawal or sudden withdrawal of study drug. All subjects were to take one tablet, twice daily, of blinded study drug for Week 57 and no drug for Week 58. Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: 578	
	NB 32 (naltrexone SR 32 mg/bupropion SR 360 mg)	Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). At the Week 56 visit subjects were re-randomized in a double-blind, 1:1 allocation ratio to undergo either tapered withdrawal or sudden withdrawal of study drug. All subjects were to take one tablet, twice daily, of blinded study drug for Week 57 and no drug for Week 58. Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: 583	
	Placebo	Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: 581	
Endpoints and definitions	Co-Primary endpoints	Applicant/FDA defined: The percent change from baseline in body weight at Week 56; The proportion of subjects who achieved ≥5% decrease from baseline body weight at Week 56. CHMP Guideline defined: The proportion of subjects with ≥10% decrease in total body weight at Week 56.	

	Secondary endpoints	Change in waist circumference, fasting triglycerides, fasting insulin, fasting HDL, IWQOL-Lite total score, HOMA-IR, hs-CRP, fasting blood glucose, fasting LDL cholesterol, systolic and diastolic blood pressure, IDS-SR total score; several QoL scores.
Database lock	29 September 2009	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The full analysis set includes all subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on LOCF method while on study drug.			
Body weight (kg), Percent change from Baseline to Endpoint	Treatment group	NB32	NB16	Placebo
	Number of subjects	471	471	511
	Baseline mean (SD)	100.17 (16.26)	100.11 (14.41)	99.29 (14.33)
	% change from baseline, LSMean (SE)	-6.14 (0.31)	-5.00 (0.31)	-1.33 (0.30)
	LS Mean difference from placebo (SE)	-4.81 (0.42)	-3.67 (0.42)	--
	95% CI	(-5.63, -3.99)	(-4.50, -2.85)	--
	p-value	< 0.001	< 0.001	

Difference between NB16 and NB32	LS Mean difference from NB16	-1.14	--	--
	95% CI	(-1.98, 0.30)	--	--
	p-value	0.008	--	--
Body Weight (kg), Proportion of subjects with≥5% Decrease from Baseline to Endpoint	**No. (%) with ≥5% decrease**	226 (47.98%)	186 (39.49%)	84 (16.44%)
	95% CI	(43.47%, 52.49%)	(35.08%, 43.91%)	(13.22%, 19.65%)
	Odds ratio vs. placebo	4.86	3.42	--
	95% confidence limit for odds ratio	(3.60, 6.57)	(2.52, 4.63)	--
	p-value	<0.001	<0.001	--

Difference between NB16 and NB32	Odds ratio vs. NB16	1.42	--	--
	95% confidence limit for odds ratio	(1.09, 1.85)	--	--
	p-value	0.010	--	--
Body Weight (kg), Proportion of subjects with≥10% Decrease from Baseline to Endpoint	**No. (%) with ≥10% decrease**	116 (24.63%)	95 (20.17%)	38 (7.44%) --
	95% CI	(20.74%, 28.52%)	16.55%, 23.79%)	(5.16%, 9.71%) --
	Odds ratio vs. placebo	4.19	3.21	--
	95% confidence limit for odds ratio p-value	(2.82, 6.23) <0.001	(2.14, 4.81) <0.001	-- --
Notes	2:1 ratio randomisation.			
Analysis description	Sensitivity analyses with ITT (Intent-to-Treat) analysis set , Completers analysis set, and (PP) Per-Protocol analysis set were conducted for all primary parameters			

In the secondary analyses when compared to placebo, NB32 was associated with favourable changes in waist circumference, blood lipids, glucose and fasting insulin as well as other biochemical markers, but not in blood pressure.

The treatment effect of NB started from week four, reached a plateau after about 6 months and was stable through the rest of 56 weeks period.

Study NB-301 also included a body composition substudy. The primary objective in this substudy was to compare the change from baseline to Week 52 in body composition, measured by total fat mass (kg) using DEXA, in the pooled active treatment groups (NB16 and NB32) compared to the placebo group. Eight study centres enrolled 77 placebo subjects and 137 NB subjects. There were 124 subjects with a baseline and post-baseline DEXA body composition measurement: 45 placebo and 79 NB. There were 58 subjects with a baseline and post-baseline abdominal CT scan: 24 placebo and 34 NB. In this substudy, the LS mean percent change in body weight from baseline was 7.18% for NB and 2.11% for placebo, and the LS mean difference between NB and placebo was 5.07% (95% CI, 7.78, -2.36).

The pooled active treatment groups showed a significantly greater decrease in total fat mass compared with placebo (p=0.001; FAS). Treatment with NB resulted in significant reductions, compared with placebo, in whole body total percent body fat (p=0.006), visceral adipose tissue mass (p=0.037), and whole body total lean mass (p=0.003).

2.5.1.2.2. Study NB-302

Study NB-302

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Programme.

Methods

The study consisted of a screening period (up to 4 weeks), a 4-week titration period, and a 52-week maintenance period. The first dose of study drug (Day 1) was to be ingested at the study centre in the presence of study centre personnel, unless there were compelling circumstances, in which case, the first dose was taken outside the study centre on Day 1. Study visits occurred every 4 weeks. Subjects were required to enroll in a closed group session beginning no later than 4 weeks post-randomization.

- **Study participants**

Eligible subjects were non smoking male or female subjects, aged 18 to 65 years, with uncomplicated obesity (body mass index [BMI] ≥30 to ≤45 kg/m^2) or subjects (BMI ≥27 to ≤45 kg/m^2) with controlled hypertension and/or dyslipidaemia. Additionally, eligible subjects had not used tobacco or tobacco products for at least 6 months before screening, were without serious medical or psychiatric illnesses, and agreed to participate in a comprehensive program of diet, exercise, and group lifestyle modification counselling plus pharmacotherapy (NB32 or placebo).

- **Treatments**

Naltrexone PR 32 mg/day and Bupropion 360 mg/day (NB32), or placebo. With regard to diet and exercise, please refer to the above section.

Behavior modification counseling sessions of 90 minutes duration began no later than 4 weeks post-randomization and were scheduled once per week for 16 weeks, once every 2 weeks for 12 weeks, and monthly thereafter for up to 28 closed-group sessions.

The diet regimen encompassing food intake was the following, and could be adjusted according to weight loss:

Body weight <200 – 249 pounds: 1200 kcal/day. 250-299 pounds: 1500 kcal/day; 300-349 pounds: 1800 kcal/day; and ≥350 pounds: 2000 kcal/day.

In addition, the following programme was prescribed: Moderate to intense exercise 30 min/day during the first 6 months; thereafter patients were encouraged to increase to 60 min moderately intense exercise.

This life style modifying programme was much more demanding in this study than in the other trials and therefore highlighted in this study. This applies both to the exercise requirements as the many focused group sessions.

- **Objectives / end points / statistical methods**

Please see above in the general introduction to the main studies.

- **Sample size**

The total sample size to be randomized was 800 subjects (3:1 randomization allocation between NB32 and placebo). A sample size of 800 subjects provided approximately 99% power to detect a statistically significant difference between NB32 and placebo for the co-primary efficacy variable, percent change from baseline on body weight. The estimate assumed a mean weight loss from baseline to Week 56 of approximately 5% for the placebo group and 10% for the NB32 group and a common standard deviation of 5% for both groups. The primary comparison between the treatment groups was made using a two-sample t-test and two-sided significance level of 5%.

Additionally, this sample size provided approximately 90% power to detect a 14% difference between NB32 (64%) and placebo (50%) based upon the additional co-primary variable, proportion of subjects with a weight decrease of ≥5% from baseline. The estimate was based upon the two-sample continuity corrected chi-square test and two-sided significance level of 5%.

The response rates for placebo were assumed to be similar to the response rates observed for the lifestyle modification alone arm.

Results

- **Baseline data**

Table 5. Selected Subject Demographics: All Randomized Subjects (Study NB-302)

Variable	Placebo (N=202)	NB32 (N=591)	Total (N=793)
Age (yrs)	n=202	n=591	n=793
Mean (SD)	45.59 (11.35)	45.89 (10.42)	45.82 (10.66)
Median	46.50	47.00	47.00
Range (minimum, maximum)	19.00, 64.00	19.00, 65.00	19.00, 65.00
Age Subgroup, n (%)			
<Total Median Value	101 (50.0%)	288 (48.7%)	389 (49.1%)
≥Total Median Value	101 (50.0%)	303 (51.3%)	404 (50.9%)
Age (yrs) Group, n (%)			
18-44	90 (44.6%)	250 (42.3%)	340 (42.9%)
45-65	112 (55.4%)	341 (57.7%)	453 (57.1%)
>65	0	0	0
Sex, n (%)			
Male	17 (8.4%)	63 (10.7%)	80 (10.1%)
Female	185 (91.6%)	528 (89.3%)	713 (89.9%)
Race, n (%)			
White	149 (73.8%)	405 (68.5%)	554 (69.9%)
Black or African American	44 (21.8%)	145 (24.5%)	189 (23.8%)
Asian	2 (1.0%)	6 (1.0%)	8 (1.0%)
Native Hawaiian or Other Pacific Islander	0	1 (0.2%)	1 (0.1%)
American Indian or Alaska Native	1 (0.5%)	7 (1.2%)	8 (1.0%)
Other	6 (3.0%)	27 (4.6%)	33 (4.2%)
Alcohol Use, n (%)			
Yes	100 (49.5%)	251 (42.5%)	351 (44.3%)
No	102 (50.5%)	340 (57.5%)	442 (55.7%)

Table 6. Other Subject Baseline Characteristics: All Randomized Subjects (Study NB-302)

Variable	Placebo (N=202)	NB32 (N=591)	Total (N=793)
BMI (kg/m^2)	n=202	n=591	n=793
Mean (SD)	36.96 (4.18)	36.34 (4.16)	36.50 (4.17)
Median	37.00	36.00	36.00
Range (minimum, maximum)	29.00, 45.00	28.00, 46.00	28.00, 46.00
BMI Subgroup, n (%)			
<Total Median Value	87 (43.1%)	275 (46.5%)	362 (45.6%)
≥Total Median Value	115 (56.9%)	316 (53.5%)	431 (54.4%)
Obesity Class, n (%)			
BMI <30 kg/m^2	1 (0.5%)	8 (1.4%)	9 (1.1%)
BMI ≥30 and <35 kg/m^2	64 (31.7%)	207 (35.0%)	271 (34.2%)
BMI ≥35 and <40 kg/m^2	79 (39.1%)	230 (38.9%)	309 (39.0%)
BMI ≥40 kg/m^2	58 (28.7%)	146 (24.7%)	204 (25.7%)
Height (cm)	n=202	n=591	n=793
Mean (SD)	165.86 (7.57)	165.74 (7.74)	165.77 (7.69)
Median	166.00	165.00	165.00
Range (minimum, maximum)	147.00, 191.00	144, 00, 197.00	144.00, 197.00
Weight (kg)	n=202	n=591	n=793
Mean (SD)	101.88 (14.96)	100.16 (15.42)	100.60 (15.31)
Median	100.00	100.00	100.00
Range (minimum, maximum)	74.00, 162.00	66.00, 159.00	66.00, 162.00
Hypertension Subgroup, n (%)			
Yes	37 (18.3%)	86 (14.6%)	123 (15.5%)
No	165 (81.7%)	505 (85.4%)	670 (84.5%)
Dyslipidemia Subgroup, n (%)			
Yes	81 (40.1%)	270 (45.7%)	351 (44.3%)
No	121 (59.9%)	321 (54.3%)	442 (55.7%)

Baseline characteristics between the two treatment groups were well balanced.

- **Numbers analysed**

Table 4. Analysis Populations: All Randomized Subjects (Study NB-302)

Analysis Set	Placebo (N=202) n (%)	NB32 (N=591) n (%)	Total (N=793) n (%)
Full Analysis Set	193 (95.5%)	482 (81.6%)	675 (85.1%)
Completers Analysis Set	106 (52.5%)	301 (50.9%)	407 (51.3%)
Per Protocol Analysis Set	92 (45.5%)	245 (41.5%)	337 (42.5%)
Safety Analysis Set	200 (99.0%)	584 (98.8%)	784 (98.9%)

The withdrawal rate is about 50%.

- **Outcomes and estimation**

The following tables summarise the primary efficacy results, i.e. the percent change in body weight from baseline to endpoint, and the proportion of subjects with body weight ≥5% Decrease from Baseline to Endpoint, and the proportion of subjects with bodyweight ≥10% decrease from baseline. Moreover, results of sensitivity testing are presented

Table 2.7.3-2 Body Weight (kg), Percent Change from Baseline to Endpoint in Study NB-302 (Full Analysis Set)

Statistic	Placebo (n=193)	NB32 (n=482)
Baseline mean (SD)	101.91 (15.04)	100.69 (15.43)
% change from baseline, LS Mean (SE)	-5.08 (0.60)	-9.29 (0.40)
LS Mean difference from placebo (SE)	--	-4.21 (0.69)
95% CI	--	(-5.56, -2.86)
p-value	--	< 0.001

Table 2.7.3-3 Sensitivity Analyses - Body Weight (kg), Least Squares Mean Percent Change from Baseline to Endpoint in Study NB-302

Percent Change in Body Weight from Baseline	Placebo	NB32
ITT Analysis Set – Endpoint	(n=196)	(n=565)
LS Mean (SE)	-4.93 (0.60)	-8.07 (0.37)
Diff of LS Mean (95% CI)		-3.15 (-4.47, -1.83)
p-value		<0.001
Completers Analysis Set – Endpoint	(n=106)	(n=301)
LS Mean (SE)	-7.25 (0.88)	-11.49 (0.57)
Diff of LS Mean (95% CI)		-4.24 (-6.09, -2.39)
p-value		<0.001
Per-Protocol Analysis Set – Endpoint	(n=92)	(n=245)
LS Mean (SE)	-7.97 (0.98)	-11.95 (0.66)
Diff of LS Mean (95% CI)		-3.98 (-6.08, -1.89)
p-value		<0.001

Table 2.7.3-4 Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint in Study NB-302 (Full Analysis Set)

Statistic	Placebo (n=193)	NB32 (n=482)
No. (%) with ≥5% decrease	82 (42.49%)	320 (66.39%)
95% CI	(35.51%, 49.46%)	(62.17%, 70.61%)
Odds ratio vs. placebo	--	2.89
95% confidence limit for odds ratio	--	(2.02, 4.13)
p-value	--	< 0.001

Table 2.7.3-5 Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥ 5% Decrease from Baseline to Endpoint in Study NB-302

Proportion of Subjects with ≥5% Decrease in Body Weight from Baseline to Endpoint	Placebo n (%)	NB32 n (%)
ITT Analysis Set	N=196	N=565
Proportion with ≥5% Decrease in Weight	84 (42.86%)	321 (56.81%)
Odds Ratio (95% CI)		1.82 (1.30, 2.56)
p-value		<0.001
Completers Analysis Set	N=106	N=301
Proportion with ≥5% Decrease in Weight	64 (60.38%)	242 (80.40%)
Odds Ratio (95% CI)		2.93 (1.78, 4.84)
p-value		<0.001
Per-Protocol Analysis Set	N=92	N=245
Proportion with ≥5% Decrease in Weight	57 (61.96%)	198 (80.82%)
Odds Ratio (95% CI)		2.96 (1.70, 5.16)
p-value		<0.001

Table 2.7.3-6 Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Endpoint in Study NB-302 (Full Analysis Set)

Statistic	Placebo (n=193)	NB32 (n=482)
No. (%) with ≥ 10% decrease	39 (20.21%)	200 (41.49%)
95% CI	(14.54%, 25.87%)	(37.10%, 45.89%)
Odds ratio vs. placebo	--	2.92
95% confidence limit for odds ratio	--	(1.95, 4.37)
p-value	--	< 0.001

Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Endpoint in Study NB-302

Percent Change in Body Weight from Baseline	Placebo n (%)	NB32 n (%)
ITT Analysis Set	N=196	N=565
Proportion with ≥10% Decrease in Weight	41 (20.92%)	199 (35.22%)
Odds Ratio (95% CI)		2.10 (1.42, 3.10)
p-value		0.0002
Completers Analysis Set	N=106	N=301
Proportion with ≥10% Decrease in Weight	32 (30.19%)	166 (55.15%)
Odds Ratio (95% CI)		3.19 (1.96, 5.20)
p-value		<0.001
Per-Protocol Analysis Set	N=92	N=245
Proportion with ≥10% Decrease in Weight	31 (33.70%)	143 (58.37%)
Odds Ratio (95% CI)		3.08 (1.82, 5.20)
p-value		<0.001

In this study with intense lifestyle modification/interventions, the results are more favourable in both treatment groups compared to the other pivotal studies. However, the difference between NB and placebo is smaller. The results are expected and underscore the effects of the life style modifications in weight reduction.

Summary of efficacy for Study NB-302This table presents the results using the FAS analysis set and LOCF as imputation method for missing data as defined by the study protocol (FAS/LOCF). However, the CHMP considered other data sets and imputation methods ((ITT/LOCF) and (Randomised Population/BOCF)) more appropriate, and this has been reflected in the SmPC.

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Program.		
Study identifier	NB-302	
Design	Randomized, Double-Blind, PBO-Controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	56 weeks: 4 weeks of titration; 52 weeks of treatment. <not applicable> <not applicable>
Hypothesis	Superiority	
Treatments groups	NB32 (naltrexone SR 32 mg/bupropion SR 360 mg)	Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). Ancillary therapy with intensive behaviour modification programme with diet instructions, prescribed exercise and group sessions. Number randomized: 591

	Placebo		Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase) Ancillary therapy with intensive behaviour modification programme.with diet instructions, prescribed exercise and group sessions. Number randomized: 202
Endpoints and definitions	Co-Primary endpoint	Applicant/FDA defined: The percent change from baseline in body weight at Week 56; The proportion of subjects who achieved ≥5% decrease from baseline body weight at Week 56. CHMP Guideline defined: Co-primary variable: Proportion of subjects with ≥10% decrease in total body weight at Week 56.	
	Secondary endpoints	Change in waist circumference, fasting triglycerides, fasting insulin, fasting HDL, IWQOL-Lite total score, HOMA-IR, hs-CRP, fasting blood glucose, fasting LDL cholesterol, systolic and diastolic blood pressure, IDS-SR total score; several QoL scores.	
Database lock	No information provided.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The full analysis set includes all subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on LOCF method while on study drug.		
Body Weight (kg), Percent Change from Baseline to Endpoint in Study NB-302	Treatment group	NB32	Placebo
	Number of subjects	482	193
	Baseline mean (SD)	100.69 (15.43)	101.91 (15.04)
	% change from baseline, LS Mean (SE)	-9.29 (0.40)	-5.08 (0.60)
	LS Mean difference from placebo (SE)	-4.21 (0.69)	--
	95% CI	(-5.56, -2.86)	--
	p-value	< 0.001	--
Body Weight (kg), Proportion of subjects with≥5% Decrease from Baseline to Endpoint	**No. (%) with ≥5% decrease;**	320 (66.39%)	82 (42.49%)
	95% CI;	(62.17%, 70.61%)	(35.51%, 49.46%)
	Odds ratio vs. Placebo	2.89	
	95% confidence limit for odds ratio	(2.02, 4.13)	
	p-value	< 0.001	
	No. (%) with ≥ 10% decrease	200 (41.49%)	39 (20.21%)

Body Weight (kg), Proportion of subjects with≥10% Decrease from Baseline to Endpoint	95% CI	(37.10%, 45.89%)	(14.54%, 25.87%)
	Odds ratio vs. Placebo	2.92	
	95% confidence limit for odds ratio	(1.95, 4.37)	
	p-value	< 0.001	
Notes	3:1 randomization		
Analysis description	Sensitivity analyses with ITT (Intent-to-Treat) analysis set , Completers analysis set, and (PP) Per-Protocol analysis set were conducted for all primary parameters		

In the secondary analyses when compared to placebo, NB32 was associated with favourable changes in waist circumference, blood lipids, glucose and fasting insulin as well as other biochemical markers, but not in blood pressure.

The treatment effect of NB started from week four, reached a plateau after about 6 months and was stable through the rest of 56 weeks period.

2.5.1.2.3. Study NB-303

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects

Methods

This was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of naltrexone SR 32 mg/bupropion SR 360 mg compared to placebo in subjects with obesity for up to 56 weeks. Beginning at Week 28 through Week 44, NB32-treated subjects who failed to achieve or maintain at least 5% body weight loss from baseline were re-randomized (1:1 ratio) to continue NB32 or begin treatment with a higher dose of naltrexone SR - naltrexone SR 48 mg/bupropion SR 360 mg (daily dose of bupropion SR was 360 mg for NB32 and NB48).

The study consisted of a screening period (up to 4 weeks), a 4-week titration period, and a 52-week maintenance period. Study visits occurred every 4 weeks.

With the purpose of safety investigations two initial dosing regimen for NB were used in a 1:1 ratio, fast or slow titration. During Week 1, the dose of naltrexone SR was 8 mg/day (fast titration) or 4 mg/day (slow titration), and the maximum dose of 32 mg/day began at Week 4 (Day 22) for the fast titration group vs. Week 5 (Day 29) for the slow titration group. For both NB groups (fast and slow), bupropion SR was initiated at a dose of 90 mg/day (Week 1) and was increased to the maximum dose of 360 mg/day at Week 4 (Day 22).

At week 56 a 1:1 re-randomisation was issued to study a sudden, respectively, tapered withdrawal, consisting of half the study dose for one week.

CHMP comments

Seemingly, the purpose of these two discontinuation schedules was to investigate the safety and tolerability of abrupt vs. tapered discontinuation.

It should be noted that the primary endpoint was at week 28 in this study with week 56 as a secondary endpoint, therefore the SmPC reflects the week 28 endpoint for the study NB303.

This trial included a sub-study (NB-303 Substudy) evaluating the change from baseline in average 24-hour systolic and diastolic blood pressure. The subject is discussed in the Safety part of the AR.

- **Study participants**

Eligible subjects were non smoking male or female subjects, aged 18 to 65 years (inclusive), with uncomplicated obesity (body mass index [BMI] ≥30 to ≤45 kg/m^2) or subjects (BMI ≥27 to ≤45 kg/m^2) with controlled hypertension and/or dyslipidaemia. Additionally, eligible subjects had not used tobacco or tobacco products for at least 6 months before screening, were without serious medical or psychiatric illnesses, and agreed to participate in a comprehensive program of diet, exercise, and group lifestyle modification counseling plus pharmacotherapy (NB32 or placebo).

- **Objectives / end points / statistical methods**

Please see above in the general introduction to the main studies.

- **Sample size**

Based on attrition rates, it was anticipated that up to 40% of randomized subjects would prematurely discontinue study drug (NB-201). The overall sample size of 1000 subjects randomized to NB32 was selected to ensure that approximately 600 subjects randomized to NB32 would complete 56 weeks of study drug treatment. To achieve the targeted number of subject-exposures at 1-year, 1000 subjects were to be randomized to NB32 and 500 subjects were to be randomized to placebo. The number of subjects treated with placebo was anticipated to provide sufficient numbers of controls in order to meaningfully evaluate, in a double-blind manner, the safety of NB32 over the 56-week period. With 1000 subjects exposed to at least one dose of NB32, there is a 99%, 98%, and 86% chance that at least one unusual AE will be observed with a true frequency of 1/100, 1/250, and 1/500, respectively. Similarly, with 600 subjects exposed to NB32 for 56 weeks, there is a 99%, 81%, and 70% chance that at least one unusual AE will be observed with a true frequency of 1/100, 1/250, and 1/500, respectively. The total sample size to be randomized was 1500 subjects (2:1 randomization allocation between NB32 and placebo). This sample size had approximately 99% power to detect a statistically significant difference between NB32 and placebo for the co-primary efficacy variables, percent change in total body weight from baseline. The estimate assumed a mean body weight decrease from baseline to Week 56 (endpoint) of approximately 1% for placebo and ≥6% for NB32 (NB-201), and a common standard deviation of 7% for both groups. The primary comparison between treatment groups was performed using a two-sample t-test and two-sided significance level of 5%. Using the same assumptions as stated above but allowing for 20% of randomized subjects not providing postbaseline data, this study had 99% power to detect a statistically significant difference between treatment groups for the co-primary efficacy endpoint, percent change in total body weight from baseline to Week 56.

This sample size also had approximately 99% power to detect a 14% difference between NB32 (64%) and placebo (50%) based upon the additional co-primary endpoint, proportion of subjects with ≥5% decrease in total body weight from baseline. This power calculation was based upon the two-sample continuity-corrected chi-square test and two-sided significance level of 5% (nQuery software, version 6). Using the same assumptions as stated above but allowing for 20% of randomized subjects not providing postbaseline data, this study had 99% power to detect a statistically significant difference between treatment groups for the co-primary efficacy endpoint, proportion of subjects with ≥5% decrease in total body weight from baseline. Response rates for placebo were assumed to be similar to the response rates observed for lifestyle modification alone.

- **Numbers analysed**

Table 4. Analysis Populations: All Randomized Subjects (Study NB-303)

Analysis Set	Placebo (N=495) n (%)	NB32/48 (N=1001) n (%)	Total (N=1496) n (%)
Full Analysis Set	456 (92.1%)	825 (82.4%)	1281 (85.6%)
Completers Analysis Set, Week 28	319 (64.4%)	619 (61.8%)	938 (62.7%)
Completers Analysis Set, Week 56	267 (53.9%)	538 (53.7%)	805 (53.8%)
Per Protocol Analysis Set	248 (50.1%)	483 (48.3%)	731 (48.9%)
Intent-to-Treat Analysis Set	474 (95.8%)	943 (94.2%)	1417 (94.7%)
Safety Analysis Set[a]	492 (99.4%)	992 (99.1%)	1484 (99.2%)

- **Outcomes and estimation**

Results of the co-primary endpoints at week 28 and the same secondary endpoint at week 56 and the CHMP Guideline defined primary endpoint are shown below:

Table 2.7.3-7 Body Weight (kg), Percent Change from Baseline to Week 28 Endpoint in Study NB-303 (Full Analysis Set)

Statistic	Placebo (n=456)	NB32 (n=825)
Baseline mean (SD)	99.29 (15.97)	100.69 (16.65)
% change from baseline, LS Mean (SE)	-1.89 (0.26)	-6.45 (0.20)
LS Mean difference from placebo (SE)	--	-4.56 (0.32)
95% CI	--	(-5.19, -3.93)
p-value	--	< 0.001

Table 2.7.3-8 Body Weight (kg), Percent Change from Baseline to Week 56 Endpoint in Study NB-303 (Full Analysis Set, Weighted LOCF)

Statistic	Placebo (n=456)	NB32 (n=702)
Baseline mean (SD)	99.29 (15.97)	100.22 (16.36)
% change from baseline, LS Mean (SE)	-1.23 (0.33)	-6.40 (0.25)
LS Mean difference from placebo (SE)	--	-5.16 (0.40)
95% CI	--	(-5.95, -4.38)
p-value	--	< 0.001

Table 2.7.3-9 Sensitivity Analyses - Body Weight (kg), Least Squares Mean Percent Change from Baseline to Week 56 Endpoint (Weighted LOCF) in Study NB-303

Percent Change in Body Weight from Baseline	Placebo	NB32
Intent-to-Treat Analysis Set (Weighted LOCF)	N=474	N=820
LS Mean (SE)	-1.24 (0.32)	-5.64 (0.23)
Diff of LS Mean (95% CI)		-4.40 (-5.15, -3.65)
p-value		<0.001
Week 56 Completers Analysis Set (Weighted LOCF)	N=267	N=434
LS Mean (SE)	-1.42 (0.48)	-8.17 (0.35)
Diff of LS Mean (95% CI)		-6.75 (-7.89, -5.60)
p-value		<0.001
Per-Protocol Analysis Set (Weighted LOCF)	N=248	N=393
LS Mean (SE)	-1.85 (0.51)	-8.46 (0.38)
Diff of LS Mean (95% CI)		-6.61 (-7.82, -5.40)
p-value		<0.001

Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Week 28 Endpoint in Study NB-303 (Full Analysis Set)

Statistic	Placebo (n=456)	NB32 (n=825)
No. (%) with ≥5% decrease	80 (17.54%)	459 (55.64%)
95% CI	(14.05%, 21.03%)	(52.25%, 59.03%)
Odds ratio vs. placebo	--	6.61
95% confidence limit for odds ratio	--	(4.95, 8.84)
p-value	--	< 0.001

Table 2.7.3-10 Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Week 56 Endpoint in Study NB-303 (Full Analysis Set, Weighted LOCF)

Statistic	Placebo (n=456)	NB32 (n=702)
Unweighted No. (%) with ≥5% decrease	78 (17.11%)	395 (56.27%)
Weighted proportion (%) with ≥5% decrease	17.11 %	50.48%
95% CI	(13.46%, 20.75%)	(46.90%, 54.07%)
Odds ratio vs. placebo	--	5.50
95% confidence limit for odds ratio	--	(4.05, 7.47)
p-value	--	< 0.001

As demonstrated in the tables above, the results of the analysis conducted at Week 56 showed comparable results to Week 28 demonstrating a greater proportion of NB32 treated subjects achieving ≥5% weight loss, including consistency in the Week 56 sensitivity analyses using the weighted procedure. Subjects receiving NB treatment for the entire 56 week period experienced the greatest treatment effects as evidenced by the completers analysis (proportion of subjects with ≥5% weight loss for NB32 was 64.9% compared with 21.7% for placebo [p<0.001].

Table 2.7.3-11 Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Week 28 in Study NB-303 (Full Analysis Set)

Statistic	Placebo (n=456)	NB32 (n=825)
No. (%) with ≥10% decrease	32 (7.02%)	225 (27.27%)
95% CI	(4.67%, 9.36%)	(24.23%, 30.31%)
Odds ratio vs. placebo	--	5.36
95% confidence limit for odds ratio	--	(3.60, 7.98)
p-value	--	< 0.001

Table 2.7.3-12 Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Week 56 in Study NB-303 (Full Analysis Set, Weighted LOCF)

Statistic	Placebo (n=456)	NB32 (n=825)
Unweighted No. (%) with ≥10% decrease	26 (5.70%)	231 (32.91%)
Weighted proportion (%) with ≥10% decrease	5.70%	28.31%
95% CI	(3.46%, 7.94%)	(25.08%, 31.54%)
Odds ratio vs. placebo	--	7.22
95% confidence limit for odds ratio	--	(4.58, 11.38)
p-value	--	< 0.001

Table 2.7.3-13 Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Week 56 (Weighted LOCF) in Study NB-303

Percent Change in Body Weight from Baseline	Placebo n (%)	NB32 n (%)
ITT Analysis Set	N=474	N=820
Unweighted Proportion with ≥10% Decrease in Weight	29 (6.12%)	230 (28.05%)
Weighted Proportion with ≥10% Decrease in Weight	6.12%	24.68%
Odds Ratio (95% CI)		5.37 (3.50, 8.25)
p-value		<0.001
Completers Analysis Set	N=267	N=434
Unweighted Proportion with ≥10% Decrease in Weight	21 (7.87%)	209 (48.16%)
Weighted Proportion with ≥10% Decrease in Weight	7.87%	39.37%
Odds Ratio (95% CI)		8.73 (5.13, 14.85)
p-value		<0.001
Per-Protocol Analysis Set	N=248	N=393
Unweighted Proportion with ≥10% Decrease in Weight	21 (8.47%)	195 (49.62%)
Weighted Proportion with ≥10% Decrease in Weight	8.47%	41.08%
Odds Ratio (95% CI)		8.30 (4.85, 14.18)
p-value		<0.001

In this study the efficacy of NB32 compared with placebo over 56 weeks of treatment was evaluated. In addition, subjects receiving NB32 therapy who did not experience or maintain at least 5% weight loss during Weeks 28 to 44 were re-randomised to continue on NB32 or increase their dose to NB48 to explore whether NB48 would be more effective than NB32 treatment. An analysis of body weight percent change from baseline to Week 56 for these re-randomised subjects did not show a meaningful difference in weight loss between the re-randomised treatment groups (NB32 and NB48, p=0.351).

Similarly, there was no meaningful difference between treatment groups (NB32 and NB48) in the proportion of subjects with ≥5% weight loss from baseline at Week 56 (p=0.585).

In conclusion, for subjects who did not respond to NB32 therapy after approximately 6 months or more of treatment, increasing the dose to NB48 did not yield differential therapeutic benefit.

Summary of efficacy for Study NB-303

This table presents the results using the FAS analysis set and LOCF as imputation method for missing data as defined by the study protocol (FAS/LOCF). However, the CHMP considered other data sets and imputation methods ((ITT/LOCF) and (Randomised Population/BOCF)) more appropriate, and this has been reflected in the SmPC.

The summary tables present the results using the FAS analysis. However the most relevant analysis care considered to be the (ITT LOCF) and randomised population BOCF.

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects.			
Study identifier	NB-303		
Design	Randomized, Double-Blind, PBO-Controlled		
	Duration of main phase:		56 weeks: 4 weeks of titration; 52-weeks of treatment. Beginning at Week 28 through Week 44, NB32-treated subjects who failed to achieve or maintain at least 5% body weight loss from baseline were re-randomized (1:1 ratio) to continue NB32 or begin treatment with a higher dose of naltrexone SR - naltrexone SR 48 mg/bupropion SR 360 mg (referred to as NB48.
	Duration of Run-in phase:		<not applicable>
	Duration of Extension phase:		<not applicable>
Hypothesis	Superiority		
Treatments groups	NB32 (naltrexone SR 32 mg/bupropion SR 360 mg)		Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: NB: 1001
	Placebo		Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase).Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized:Placebo: 495
Endpoints and definitions	Co-Primary endpoints	Applicant/FDA defined: The percent change from baseline in body weight at Week 28.The proportion of subjects who achieved ≥5% decrease from baseline body weight at Week 28.CHMP Guideline defined: Co-primary variable: Proportion of subjects with ≥10% decrease in total body weight at Week 28.	
	Secondary endpoints	Change in waist circumference, fasting triglycerides, fasting insulin, fasting HDL, IWQOL-Lite total score, HOMA-IR, hs-CRP, fasting blood glucose, fasting LDL cholesterol, systolic and diastolic blood pressure, IDS-SR total score; several QoL scores.	
Database lock	25 August 2009.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The full analysis set includes all subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on LOCF method while on study drug.		
Body weight (kg), Percent change from Baseline to Endpoint	Treatment group	NB32	Placebo
	Number of subject	825	456
	Baseline mean (SD)	100.69 (16.65)	99.29 (15.97)
	% change from baseline, LS Mean (SE)	-6.45 (0.20)	-1.89 (0.26)
	LS Mean difference from placebo (SE)	-4.56 (0.32)	--
	95% CI	-5.19, -3.93)	--
	p-value	< 0.001	--
Body Weight (kg) Proportion of subjects with ≥5% Decrease from Baseline to Endpoint	**No. (%) with ≥5% Decrease**	459 (55.64%)	80 (17.54%)
	95% CI	(52.25%, 59.03%)	(14.05%, 21.03%)
	Odds ratio vs. Placebo	6.61	--
	95% confidence limit for odds ratio	(4.95, 8.84)	--
	p-value	< 0.001	--
Body Weight (kg), Proportion of subjects with≥10% Decrease from Baseline to Endpoint	**No. (%) with ≥10% decrease**	225 (27.27%)	32 (7.02%)
	95% CI	(24.23%, 30.31%)	(4.67%, 9.36%)
	Odds ratio vs. Placebo	5.36	--
	95% confidence limit for odds ratio	(3.60, 7.98)	--
	p-value	< 0.001	--
Notes	2:1 ratio randomisation in main the 28 weeks study. No meaningful differences in weight loss between NB32 and NB48 re-randomized groups were seen.		
Analysis description	Sensitivity analyses with ITT (Intent-to-Treat) analysis set, Completers analysis set, and (PP) Per-Protocol analysis set were conducted for all primary parameters.		

In the secondary analyses when compared to placebo, NB32 was associated with favourable changes in waist circumference, blood lipids, glucose and fasting insulin as well as other biochemical markers, but not in blood pressure.

2.5.1.2.4. Study NB-304

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release/Bupropion 360 mg Sustained Release and Placebo in Obese Subjects with Type 2 Diabetes Mellitus

Methods

This was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of NB32 compared to placebo over 56 weeks in approximately 525 overweight and obese subjects with type 2 diabetes.

The study consisted of a screening period (up to 4 weeks), a 4-week titration period, and a 52-week maintenance period. Subjects were to self-monitor blood glucose for the first 4 weeks after randomization, or longer, if warranted in the judgment of the investigator. All subjects received ancillary therapy at baseline and Weeks 4, 16, 28, and 40 consisting of diet instruction, advice on behaviour modification, and physical activity suggestions.

- **Study participants**

Eligible subjects were overweight and obese (BMI ≥27 to ≤45 kg/m^2), smoking and nonsmoking, 18 to 70 year-old (inclusive) males and females diagnosed with type 2 diabetes mellitus (HbA1c >7% and <10%; fasting blood glucose <270 mg/dL) on no injectable antidiabetes medication or inhaled insulin for more than 3 months. Additionally, eligible subjects were without serious medical or psychiatric illnesses, and received stable doses of oral single or combination hypoglycaemic medications for at least 3 months prior to randomization or did not take medications for the treatment of type 2 diabetes mellitus.

As patients for this study only were eligible if they were diagnosed with type 2 diabetes, they differed markedly from the patients in the other pivotal studies.

- **Objectives / statistical methods**

Please see above in the general introduction to the main studies.

- **Outcomes / endpoints**

The primary and secondary endpoints were the same as in the other pivotal studies. In addition, this study also investigated HbA1c, proportion of subjects with HbA1c <7%, percent of subjects requiring rescue medications for diabetes, percent of subjects requiring change in dose(s) of oral antidiabetes medication, proportion of subjects with HbA1c <6.5%, percent of subjects discontinuing due to poor glycaemia control,

- **Sample size**

The total sample size to be randomized was approximately 525 subjects (2:1 randomization allocation between NB32 and placebo). A sample size of 525 subjects was to provide approximately 99% power to detect a statistically significant difference between NB32 and placebo for the co-primary efficacy variable, percent change in body weight from baseline. The estimate assumed a mean weight loss from baseline to Week 56 of approximately 1.5% for the placebo group and ≥6.5% for the NB32 group and a common SD of 5% for both groups. The primary comparison between the treatment groups used a two-sample t-test and two-sided significance level of 5%. Using the same assumptions as stated above but allowing for 20% of randomized subjects not providing postbaseline data, the study had 99% power to detect a statistically significant difference between treatment arms for the co-primary efficacy endpoint, percent change in body weight from baseline to Week 56.

The sample size also had approximately 88% power to detect a statistically significant difference between treatment arms for the co-primary endpoint of body weight decrease of ≥5% from baseline.

This power calculation was made assuming a body weight decrease of ≥5% from baseline at the Week 56 visit will be observed for 15% of subjects randomized to placebo and for 27.5% of subjects randomized to combination treatment. This comparison was made using a two-sample continuity corrected chi-square test and two-sided significance level of 5%.

Results

Baseline characteristics

Table 6. Selected Subject Demographics: All Randomized Subjects (Study NB-304)

Variable	Placebo (N=170)	NB32 (N=335)	Total (N=505)
Age (yrs)			
Mean (SD)	53.46 (9.83)	54.02 (9.05)	53.83 (9.32)
Median	54.00	55.00	54.00
Range (minimum, maximum)	27.00, 70.00	20.00, 72.00	20.00, 72.00
Age Subgroup, n (%)			
<Total Median Value	79 (46.5%)	149 (44.5%)	228 (45.1%)
≥ Total Median Value	91 (53.5%)	186 (55.5%)	277 (54.9%)
Age (yrs) Group, n (%)			
18-44	33 (19.4%)	50 (14.9%)	83 (16.4%)
45-64	112 (65.9%)	249 (74.3%)	361 (71.5%)
≥65	25 (14.7%)	36 (10.7%)	61 (12.1%)
Sex, n (%)			
Male	80 (47.1%)	140 (41.8%)	220 (43.6%)
Female	90 (52.9%)	195 (58.2%)	285 (56.4%)
Race, n (%)			
White	140 (82.4%)	261 (77.9%)	401 (79.4%)
Black or African American	18 (10.6%)	63 (18.8%)	81 (16.0%)
Asian	5 (2.9%)	7 (2.1%)	12 (2.4%)
Native Hawaiian or Other Pacific Islander	0	1 (0.3%)	1 (0.2%)
American Indian or Alaska Native	2 (1.2%)	2 (0.6%)	4 (0.8%)
Other	5 (2.9%)	1 (0.3%)	6 (1.2%)
Tobacco Use, n (%)			
Current Smoker	15 (8.8%)	38 (11.3%)	53 (10.5%)
Former Smoker or Nonsmoker	155 (91.2%)	297 (88.7%)	452 (89.5%)
Alcohol Use, n (%)			
Yes	69 (40.6%)	96 (28.7%)	165 (32.7%)
No	101 (59.4%)	239 (71.3%)	340 (67.3%)

Table 7. Other Subject Baseline Characteristics: All Randomized Subjects (Study NB-304)

Variable	Placebo (N=170)	NB32 (N=335)	Total (N=505)
BMI (kg/m^2)			
Mean (SD)	36.40 (4.50)	36.40 (4.75)	36.40 (4.66)
Median	37.00	36.00	36.00
Range (minimum, maximum)	27.00, 46.00	27.00, 46.00	27.00, 46.00
BMI Subgroup, n (%)			
< Total Median Value	70 (41.2%)	152 (45.4%)	222 (44.0%)
≥ Total Median Value	100 (58.8%)	183 (54.6%)	283 (56.0%)
Obesity Class, n (%)			
BMI <30 kg/m^2	11 (6.5%)	18 (5.4%)	29 (5.7%)
BMI ≥30 and <35 kg/m^2	49 (28.8%)	111 (33.1%)	160 (31.7%)
BMI ≥35 and <40 kg/m^2	64 (37.6%)	110 (32.8%)	174 (34.5%)
BMI ≥40 kg/m^2	46 (27.1%)	96 (28.7%)	142 (28.1%)
Height (cm)			
Mean (SD)	169.65 (9.65)	168.87 (10.06)	169.13 (9.92)
Median	170.00	168.00	168.00
Range (minimum, maximum)	145.00, 193.00	147.00, 194.00	145.00, 194.00
Weight (kg)			
Mean (SD)	105.08 (16.99)	104.22 (18.93)	104.51 (18.28)
Median	105.00	103.00	104.00
Range (minimum, maximum)	67.00, 154.00	64.00, 167.00	64.00, 167.00
Hypertension Subgroup, n (%)			
Yes	103 (60.6%)	212 (63.3%)	315 (62.4%)
No	67 (39.4%)	123 (36.7%)	190 (37.6%)
Dyslipidemia Subgroup, n (%)			
Yes	145 (85.3%)	280 (83.6%)	425 (84.2%)
No	25 (14.7%)	55 (16.4%)	80 (15.8%)

- **Outcomes and estimation**

Results from the co- primary endpoints as defined by the FDA and by the CHMP guideline are shown below, together with s sensitivity analyses:

Table 2.7.3-14 Body Weight (kg), Percent Change from Baseline to Endpoint in Study NB-304 (Full Analysis Set)

Statistic	Placebo (n=159)	NB32 (n=265)
Baseline mean (SD)	104.99 (17.13)	106.35 (19.11)
% change from baseline, LS Mean (SE)	-1.75 (0.43)	-5.03 (0.34)
LS Mean difference from placebo (SE)	--	-3.28 (0.54)
95% CI	--	(-4.34, -2.22)
p-value	--	< 0.001

Table 2.7.3-15 Sensitivity Analyses - Body Weight (kg), Least squares Mean Percent Change from Baseline to Endpoint in Study NB-304

Percent Change in Body Weight from Baseline	Placebo	NB32
ITT Analysis Set	(n=166)	(n=321)
LS Mean (SE)	-1.70 (0.41)	-3.69 (0.30)
Diff of LS Mean (95% CI)		-2.00 (-2.98, -1.01)
p-value		<0.001
Completers Analysis Set	(n=100)	(n=175)
LS Mean (SE)	-2.18 (0.62)	-5.86 (0.47)
Diff of LS Mean (95% CI)		-3.68 (-5.18, -2.18)
p-value		<0.001
Per-Protocol Analysis Set	(n=102)	(n=149)
LS Mean (SE)	-1.95 (0.61)	-6.11 (0.51)
Diff of LS Mean (95% CI)		-4.16 (-5.70, -2.62)
p-value		<0.001

Table 2.7.3-16 Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint in Study NB-304 (Full Analysis Set)

Statistic	Placebo (n=159)	NB32 (n=265)
No. (%) with ≥5% decrease	30 (18.87%)	118 (44.53%)
95% CI	(12.79%, 24.95%)	(38.54%, 50.51%)
Odds ratio (vs. placebo)	--	3.44
95% confidence limit for odds ratio	--	(2.15, 5.50)
p-value	--	< 0.001

Table 2.7.3-17 Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint in Study NB-304

Proportion of Subjects with ≥5% Decrease in Body Weight from Baseline to Endpoint	Placebo n (%)	NB32 n (%)
ITT Analysis Set	N=166	N=321
Proportion with ≥5% Decrease in Weight, n (%)	30 (18.07%)	115 (35.83%)
Odds Ratio (95% CI)		2.51 (1.59, 3.97)
p-value		<0.001
Completers Analysis Set	N=100	N=175
Proportion with ≥5% Decrease in Weight, n (%)	24 (24.00%)	93 (53.14%)
Odds Ratio (95% CI)		3.72 (2.13, 6.47)
p-value		<0.001
Per-Protocol Analysis Set	N=102	N=149
Proportion with ≥5% Decrease in Weight, n (%)	25 (24.51%)	82 (55.03%)
Odds Ratio (95% CI)		4.03 (2.29, 7.09)
p-value		<0.001

Table 2.7.3-18 Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Endpoint in Study NB-304 (Full Analysis Set)

Statistic	Placebo (n=159)	NB32 (n=265)
No. (%) with ≥10% decrease	9 (5.66%)	49 (18.49%)
95% CI	(2.07%, 9.25%)	(13.82%, 23.16%)
Odds ratio (vs. placebo)	--	3.75
95% confidence limit for odds ratio	--	(1.79, 7.88)
p-value	--	< 0.001

Table 2.7.3-19 Sensitivity Analyses - Body Weight (kg), Proportion of Subjects with ≥10% Decrease from Baseline to Endpoint in Study NB-304

Proportion of Subjects with ≥10% Decrease in Body Weight from Baseline to Endpoint	Placebo n (%)	NB32 n (%)
ITT Analysis Set	N=166	N=321
Proportion with ≥10% Decrease in Weight, n (%)	9 (5.42%)	49 (15.26%)
Odds Ratio (95% CI)		3.10 (1.48, 6.48)
p-value		0.003
Completers Analysis Set	N=100	N=175
Proportion with ≥10% Decrease in Weight, n (%)	8 (8.00%)	46 (26.29%)
Odds Ratio (95% CI)		4.23 (1.90, 9.44)
p-value		0.0004
Per-Protocol Analysis Set	N=102	N=149
Proportion with ≥10% Decrease in Weight, n (%)	8 (7.84%)	43 (28.86%)
Odds Ratio (95% CI)		5.03 (2.24, 11.32)
p-value		<0.001

Although statistically significant, the difference in weight loss between NB32 and placebo in is generally less in this study in patients with type 2 diabetes compared to the other pivotal studies enrolling non-diabetic patients.

Summary of efficacy for Study NB-304

This table presents the results using the FAS analysis set and LOCF as imputation method for missing data as defined by the study protocol (FAS/LOCF). However, the CHMP considered other data sets and imputation methods ((ITT/LOCF) and (Randomised Population/BOCF)) more appropriate, and this has been reflected in the SmPC.

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release/Bupropion 360 mg Sustained Release and Placebo in Obese Subjects with Type 2 Diabetes Mellitus		
Study identifier	NB-304	
Design	Randomized, Double-Blind, PBO-Controlled	
	Duration of main phase:	56 weeks: 4 s of week titration; 52 weeks of treatment.
	Duration of Run-in phase:	<not applicable>
	Duration of Extension phase:	<not applicable>
Hypothesis	Superiority	

Treatments groups	NB32 (naltrexone SR 32 mg/bupropion SR 360 mg)		Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: NB32:335
	Placebo		Treatment: A 4-week titration schedule followed by a maintenance dose of 2 tablets b.i.d. for 52 weeks (maintenance phase). Ancillary therapy with diet instructions, behaviour modification and exercise. Number randomized: Placebo:170
Endpoints and definitions	Co-Primary endpoints	Applicant/FDA defined: The percent change from baseline in body weight at Week 28. The proportion of subjects who achieved ≥5% decrease from baseline body weight at Week 56. CHMP Guideline defined: Co-primary variable: Proportion of subjects with ≥10% decrease in total body weight at Week 56.	
	Secondary endpoints	HbA1c, fasting triglycerides, fasting HDL, fasting blood glucose, waist circumference, proportion of subjects with ≥10% decrease in total body weight, proportion of subjects with HbA1c <7%, percent of subjects requiring rescue medications for diabetes, percent of subjects requiring change in dose(s) of oral antidiabetes medication, HOMA-IR, fasting insulin, proportion of subjects with HbA1c <6.5%, IWQOL-Lite total score, hs-CRP, percent of subjects discontinuing due to poor glycemic control, fasting low-density lipoprotein (LDL) cholesterol, systolic and diastolic blood pressure, several QoL scores.	
Database lock	No information provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The full analysis set includes all subjects who were randomised, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on LOCF method while on study drug.		
	Treatment group	NB32	Placebo
	Number of subject	265	159
Body Weight (kg), Percent Change from Baseline to Endpoint	Baseline mean(SD)	106.35 (19.11)	104.99 (17.13)
	% change from baseline, LS Mean (SE)	-5.03 (0.34)	-1.75 (0.43)
	LS Mean difference from placebo (SE)	-3.28 (0.54)	--
	95% CI	(-4.34, -2.22)	--
	p-value	< 0.001	--
Body Weight (kg), Proportion of Subjects	**No. (%) with ≥5% decrease**	118 (44.53%)	30 (18.87%)

with ≥5% Decrease from Baseline to Endpoint	95% CI	(38.54%, 50.51%)	(12.79%, 24.95%)
	Odds ratio (vs. placebo)	3.44	--
	95% confidence limit for odds ratio	(2.15, 5.50)	--
	p-value	< 0.001	--
Body Weight (kg), Proportion of subjects with≥10% Decrease from Baseline to Endpoint	**No. (%) with ≥10% decrease**	49 (18.49%)	9 (5.66%)
	95% CI	(13.82%, 23.16%)	(2.07%, 9.25%)
	Odds ratio (vs. placebo)	3.75	--
	95% confidence limit for odds ratio	(1.79, 7.88)	--
	p-value	< 0.001	--
Notes	2:1 ratio randomisation. Evaluation of the glycaemic control in these obese patients with type 2 diabetes showed that at endpoint, subjects receiving NB32 had statistically significantly greater changes from baseline in HbA1c (LS mean change NB32 -0.63% vs. -0.14% for placebo; p<0.001). The magnitude of the treatment difference (NB32 minus placebo) was -0.49% (95% CI, -0.71 to -0.27).		
Analysis description	Sensitivity analyses with ITT (Intent-to-Treat) analysis set, Completers analysis set, and (PP) Per-Protocol analysis set were conducted for all primary parameters.		

The biochemistry variables investigated in the other pivotal studies have in this study been supplemented with variables addressing glycaemic control in more detail.

Effects on lipids and glycaemic parameters were generally more favourable in patients receiving NB32 than placebo patients.

Clinical studies in special populations

The study in patients with type 2 diabetes is presented and assessed in the above section (Study NB-304).

2.5.2. Analysis performed across trials (pooled analyses AND meta-analysis)

Data from the four Phase 3 studies were pooled to investigate the effects on subpopulations of treatment with NB (both 16 mg in Study NB-301 and 32 mg from all studies) compared with placebo and NB32 compared with placebo. They are described hereafter.

1) Demographic Subgroups

The subject demographic subgroups included:

- Sex: Male, Female.
- Race: White, Black, and Other.
- Age: 18-44, 45-64, and ≥65 years.
- BMI: <30, 30 to <35, 35 to <40, ≥40 kg/m^2.

The comparisons of NB pooled (16 and 32 mg) to placebo and NB32 to placebo were analysed for each demographic subgroup for the primary variables of percent decrease from baseline in body weight and the proportion of subjects with a weight loss from baseline of ≥5%.

The comparisons of NB pooled (16 and 32 mg) to placebo in the percent decrease from baseline in body weight showed that for all the subgroups (based on sex, race, age, and BMI), NB was generally more effective than placebo. A marginal treatment by sex interaction (p=0.096) and a treatment by race interaction (p<0.001) suggested a greater reduction in weight for females and the White race. A treatment by BMI interaction (p=0.040) suggested a greater reduction in weight for subjects with BMI <30 kg/m^2 (n=55). This was not observed in the interim analysis of the ongoing cardiovascular outcome study (NB-CVOT) and thus not reflected in the SmPC (see discussion later).

For the age range of 45-64 subgroup, the LS mean difference from placebo was the same for both NB and NB32 and for BMI < 30, where the NB Pooled subgroup had slightly greater LS mean difference from placebo than the NB32 subgroup. The comparisons of NB32 with placebo in the percent decrease from baseline in body weight showed that for all the subgroups (based on sex, race, age, and BMI), NB32 was more effective than placebo.

The comparisons of NB pooled (16 and 32 mg) to placebo in the proportion of subjects with a weight loss from baseline of ≥5% showed that for all the subgroups (based on sex, race, age, and BMI), NB was more effective than placebo. There was no treatment by subgroup interactions.

The results were similar for the NB32 to placebo comparison for subgroups. The differences from placebo were numerically greater for all subgroups, when pooling the data of the higher dose only (NB32) compared with both doses NB (16 and 32) suggesting a greater treatment effect with NB32. There was no treatment by subgroup interactions.

2) Baseline Characteristics Subgroups

Hypertension, Dyslipidaemia, Metabolic Syndrome, Impaired Fasting Glucose

The baseline disease characteristics were based on the presence or absence of hypertension, dyslipidaemia, metabolic syndrome, and impaired fasting glucose (defined as glucose ≥100 mg/dL at baseline). The comparisons of NB pooled to placebo and NB32 to placebo were analysed for each baseline disease characteristic for the primary variables of percent decrease from baseline in body weight and the proportion of subjects with ≥5% weight loss from baseline.

For all the subgroups based on the presence or absence of baseline diseases, NB was more effective than placebo in the percent change in weight from baseline. There was a marginal treatment by hypertension interaction (p=0.064) and a significant treatment by impaired fasting glucose interaction (p=0.014) suggesting a greater reduction in weight for subjects without hypertension and without impaired fasting glucose.

The results were similar for the NB32 to placebo comparison for subgroups based on the presence or absence of baseline diseases. The differences from placebo were numerically greater for all subgroups when pooling the data of the higher dose only (NB32) compared with both doses pooled (NB) suggesting a greater treatment effect with NB32. A treatment by hypertension interaction (p=0.054) and treatment by impaired baseline fasting blood glucose interaction (p=0.007) suggested a greater reduction in weight for subjects without hypertension and without impaired glucose tolerance at baseline.

For all the subgroups based on the presence or absence of baseline diseases, NB was more effective than placebo in the proportion of subjects with a ≥5% weight loss from baseline. There were no treatment by subgroup interactions.

The results were similar for the NB32 to placebo comparison based on the presence or absence of baseline diseases. The differences from placebo were slightly greater for all subgroups when pooling the data of the higher dose only (NB32) compared with both doses (NB) suggesting a greater treatment effect with the higher dose. For the NB32 data, in contrast to the NB data, there was a marginal treatment by subgroup interaction for dyslipidaemia (p=0.093) and for impaired fasting glucose (p=0.068) suggesting potentially greater probability of ≥5% weight loss in subjects with dyslipidaemia at baseline and without impaired fasting glucose at baseline. In all subgroups, the proportion of subjects experiencing ≥5% weight loss from baseline was greater than 45% (49.8% to 55.7%) and more than double the proportion observed with placebo treatment (19.5% to 23.4%).

Smoking Status

For both subgroups based on smoking status (current smoker versus former or non-smoker), NB was more effective than placebo in the percent change in weight from baseline. There was no treatment by smoking status interaction. The results were similar for the NB32 to placebo comparison for smoking status subgroups. The treatment difference of NB32 from placebo was slightly higher than observed with NB indicating the higher dose was more effective.

For both subgroups based on smoking status, NB was more effective than placebo in proportion of subjects with a weight loss from baseline of ≥5%. There was no treatment by smoking status interaction. The results were similar for the NB32 to placebo comparison for smoking status subgroups. The treatment difference of NB32 from placebo was slightly higher than observed with NB indicating the higher dose was more effective.

2.5.3. Supportive studies

2.5.3.1. Study NB-431

Study NB-431 was a Phase 2, double-blind, placebo-controlled, randomized, outpatient study to assess brain function using fMRI methods in 46 healthy overweight/obese female subjects. fMRI imaging methods were used to assess the effects of NB on the response to food cues under fasting and fed conditions at one month of treatment. Compared to the placebo group, the NB32 group had enhanced activation following exposure to food cues in the dorsal anterior cingulate, superior frontal, posterior insula, hippocampal and superior parietal regions, which are brain regions involved in inhibitory control, internal awareness, memory/conditioning and somatosensory processing respectively.

2.5.3.2. Study NB-401

Study NB-401 was an open-label study, conducted in subjects who were smokers and were overweight or had uncomplicated obesity or obesity associated with controlled hypertension or dyslipidemia, investigated the efficacy and safety of treatment with naltrexone SR 32 mg/bupropion SR 360 mg daily combined with behavior modification counseling. The treatment showed efficacy in achieving smoking cessation without an increase in nicotine withdrawal symptoms, and, at the same time, limited weight gain after quitting. Subjects who quit smoking had a small increase from baseline weight at Week 12 (0.08%) and Week 24 (1.32%) when compared to subjects who were still smoking. Mean weight change from baseline value at Weeks 12 and Week 24 was not meaningfully different in subjects who quit smoking.

2.5.3.3. Study NB-402

Study NB-402 was an exploratory, open-label, single-center study with a single treatment group that evaluated the efficacy and safety of NB32 in overweight or obese subjects who had major depression, and who may have been diagnosed with controlled hypertension and/or dyslipidemia, but were without other serious medical or psychiatric illness. All subjects participated in ancillary therapy that consisted of diet instruction, advice on diet behavior modification, and a prescription for exercise. Of the 25 subjects enrolled, 13 (52.0%) completed all 24 weeks of study treatment. Depressive symptoms decreased in a clinically meaningful way in this open-label study following treatment with NB32 and ancillary therapy. Mean percent decreases in total body weight and mean decreases in BES scores, IDS-SR scale, serum leptin concentrations, and the majority of individual COE question scores from baseline to endpoint at Weeks 12 and 24 (LOCF) were also apparent.

2.5.3.4. Study CVOT (Light trial)

Study NB-CVOT is a double-blind, randomised, placebo-controlled study designed to assess the effect of NB32 versus placebo on the occurrence of MACE, defined as CV death, nonfatal stroke, or nonfatal myocardial infarction (MI). The study is ongoing, and interim results have been provided with the D120 response. 8910 patients have been randomised into the treatment period of the study. The study population was older and exhibited a higher proportion of CV risk factors compared to the Phase 3 studies. Mean age was 61.0 years, and 54.5% were females. Mean BMI was 37.3 kg/m2. One third (32.1%) had CV disease, 85.2% had type 2 diabetes (T2DM), 91.8% had dyslipidaemia and 92.3% had hypertension. 26.9% had an eGFR <90 mL/min. The proportion of patients achieving a weight loss of >10% showed a tendency to increase with increasing BMI: BMI <35 kg/m2: 10.9%; BMI: ≥35 to <40 kg/m2: 11.8%; BMI ≥40 kg/m2: 14.8%. The result was consistent with the results from the Phase 3 trials for BMI >30 kg/m2. Key results on cardiovascular outcomes are discussed in the safety section of this report.

The CVOT trial is currently ongoing and a further analysis is planned after 50% of MACE events.

2.5.4. Discussion on clinical efficacy

- Choice of the dose and rationale for the Fixed Dose Combination

Initially, the CHMP considered that the proposed fixed dose combination had not been adequately investigated in terms of superiority over the monocomponents. Study OT-101 was negative in that respect, and it was debated whether firm conclusions could be drawn from Study NB-201. This issue was raised due to a concern that the therapeutic contribution of each individual component at the exact dose used in the combination was not clearly shown relative to the combination. The Applicant has justified this by reiterating the rationale for the combination, reviewing the results of study NB201, and by detailing the PK and PD data used to bridge the Phase 2 dose combinations to the doses and formulations used in Phase 3.

The CHMP accepts the rationale for the combination of bupropion (which results in release of α-MSH and has an anorexic effect) with naltrexone (to block the negative feedback from β-endorphin on release of α-MSH), and as such, agrees that naltrexone alone has no effect on weight-loss. The design of study NB201 is therefore acceptable, and it is agreed that the combination was more effective than bupropion alone. The selection of the 32 mg naltrexone dose is also accepted on the grounds of balancing efficacy with tolerability.

The changes made between Phase 2 and 3, in the formulation of naltrexone (from immediate release to prolonged release) and the dose of bupropion (from 400 to 360 mg) have been justified on rational clinical grounds. The steady state PK of 360 mg/day bupropion remains unclear, but any minor

difference in exposure with the lower dose is unlikely to influence the efficacy, which was investigated separately in the pivotal studies anyway. The rationale for the FDC is therefore accepted.

In the following sections clinical efficacy as evidenced from the four pivotal Phase 3 studies (NB-301, NB-302, NB-303 and NB-304) is discussed.

- ***Design and conduct of clinical studies***

The pivotal studies were randomised, double-blind, multicentre, placebo-controlled studies conducted in obese and overweight subjects receiving customary diet and behavioural counselling, including prescribed exercise (Studies NB-301 and NB-303) and in obese/overweight subjects undergoing intensive lifestyle modification counselling (Study NB-302). One study was conducted in obese/overweight subjects with type 2 diabetes (Study NB-304). Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI ≥30 and ≤45 kg/m^2 for subjects with uncomplicated obesity and with a BMI of ≥27 and ≤45 kg/m^2 for overweight or obese subjects with controlled hypertension and/or dyslipidaemia. The type 2 diabetes patients enrolled in Study NB-304 were to have a BMI ≥27 to ≤45 kg/m^2. Treatment duration in all studies was 56 weeks.

It is a significant weakness that the Phase 3 programme was not tailored to also include elderly patients in sufficient numbers. However, some safety data are available from older patients in the NB-CVOT study. The limitations of the data are reflected in the SmPC, by mentioning the use with caution in patients over 65 years of age. In addition, in patients 75 years of age, the use of NB is not recommended.

The study design employed in all studies is considered to be acceptable with regard to randomisation, blinding and treatment duration.

The application of diet and exercise programmes in all treatments arms of all studies and with an intensive programme in one of the studies (NB-302) is supported.

The BMI cut-off values for patients with uncomplicated obesity and overweight/obese patients with co-morbid conditions are acceptable.

No run-in period where patients enrolled in the studies should have been subjected to an appropriate weight reducing diet for a specified minimum time have been implemented as recommended in the CHMP guideline. This omission is however considered acceptable by the CHMP.

More importantly, the studies were not designed to ensure that patients participating in these studies should have follow up examinations for a period deemed appropriate to assess rebound effects and the effect of drug cessation on appetite and weight control. Therefore, it is not known from the Phase 3 studies whether any weight loss accomplished after e.g. one-year treatment with NB is maintained upon cessation of therapy because an adequate follow-up period after the treatment period was not part of the study design. However, interim data from study NB-CVOT, which included follow-up for a longer period following cessation of therapy, suggest that termination of NB therapy is associated with a significant weight gain, but it is unclear whether over the longer term this would result in a rebound beyond levels observed at baseline.

None of the pivotal studies include an active reference. Orlistat is the only weight control medicine widely available in the EU. This medicine is associated with very common adverse reactions of a distinct, gastrointestinal nature (such as flatus with discharge, faecal urgency and fatty oily stool) which makes it difficult to blind this medicine if included as an active reference. For this reason, the omission of an active reference is acceptable.

The following FDA-recommended primary efficacy endpoints were employed for all four Phase 3 studies:

- The percent change from baseline in body weight at Week 56 (Last Observation Carried Forward [LOCF]) for Studies NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for Study NB-303.
- The proportion of subjects who achieved ≥ 5% decrease from baseline body weight at Week 56 (LOCF) for studies NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for study NB-303.

Despite the fact that the responder criterion employed in the co-primary endpoint (≥ 5% decrease) is not concordant with the CHMP-recommended (≥ 10%), the ≥ 10% criterion is included as pre-specified secondary endpoint. This is acceptable by the CHMP.

The primary and secondary endpoints included in the studies are considered adequate to evaluate the efficacy of a medicine in weight control.

The primary analysis was based on the full analysis set (FAS) and using LOCF as imputation method for missing data. However, the studies are characterised by a high drop-out rate (about half of the patients discontinued prematurely). It can be discussed if LOCF is a sufficiently conservative imputation method, and the sensitivity analyses have an important role in substantiating the results of the primary analysis because drop-outs may very well be different from completers in terms of efficacy.

The Applicant has conducted a number of sensitivity analyses: Analyses of the ITT analysis set (slightly different from the FAS), the completers set and the per protocol set as wells as analysis of repeated measures mixed effects model for the continuous endpoint and an analysis using baseline observation carried forward (BOCF) in the all-randomised set as imputation method for missing data. In particular, the BOCF is considered well suited as supplemental analysis in view of the high drop-out rate and the restricted nature of the primary analysis set (which excludes patients without an on-treatment post-baseline measurement). Further analyses using the BOCF have been provided.

The Applicant objected to present the efficacy results in the SmPC using BOCF, but proposed to maintain the LOCF using a more conservative analysis set (ITT dataset) for the mean weight loss results (with adherence rates included in the text), whilst using the BOCF for the responder analyses. This is acceptable for the CHMP.

- ***Efficacy data and additional analyses***

Overall, the main findings in the pivotal studies were that treatment with NB32 (and NB16 in Study NB 301) resulted in statistically significant weight loss compared with placebo in overweight/obese subjects with or without hypertension or dyslipidaemia (Studies NB-301, NB-302, and NB 303), as well as in overweight/obese patients with type 2 diabetes mellitus (Study NB 304). Week 56 results for Study NB 303 should be interpreted with caution because of the re-randomisation of active non-responders to NB32 or NB48 at week 28.

Mean weight change over a treatment duration of about one year in NB32-treated subjects in Studies NB-301, NB-303, and NB-304 ranged from approximately -6.5 to -5.0% compared to -1.8 to -1.2% for placebo (FAS, LOCF). In the all-randomised set using BOCF, the effect of NB32 in those studies ranged from -4.4 to -3.1% and the effect of placebo ranged from -1.3 to -0.8%.

In patients with intensive behaviour modification counselling in NB-302, the weight loss was higher in both treatment groups (9.3% for NB32 and 5.1% for placebo), (FAS, LOCF). This was also true for the all-randomised set with BOCF (-5.9% for NB32 and -4.0% for placebo).

The mean differences from placebo (treatment differences) in percent weight loss ranged from -3.3% (Study NB-304) to -5.2% (Study NB-303) at Week 56 but using the all-randomised set and BOCF, this was -1.7% in study NB 304 and -3.7% in study NB 303. The treatment differences were lowest in

patients with type 2 diabetes (Study NB-304) and in patients with intensive behaviour modification (Study NB-302).

The weight loss on NB32 was modest-moderate as mean weight changes from baseline was less than 10 % in all studies, and the difference to placebo did not exceed 5% in any study (all-randomised set, BOCF).

The Applicant has performed an examination of treatment-by-BMI interaction for the Phase 3 studies and demonstrated that for the primary endpoint (i.e. weight change from baseline) the greatest difference between NB and placebo therapy was observed in patients with a BMI <30 kg/m2. This is not entirely what would be expected. A similar pattern was seen for the ≥ 5% weight loss categorical endpoint although this was not significant. Hence, the data from the Phase 3 studies indicated that the efficacy of NB may be less in patients with the highest BMI. However, interim data from the ongoing NB-CVOT study with considerably larger patient numbers show a tendency to a higher proportion of patients achieving a weight loss of >10% with increasing BMI. Consequently, it is reasonable to conclude that NB causes clinically relevant weight loss also in patients in the high BMI groups.

The effect of NB was detectable at week 4, reached a plateau after approximately 6 months and remained throughout the rest of the study in patients who continued with treatment. The plateau was also seen in patients continuing treatment in the placebo group where the subjects did not appear to return to baseline weight, but following a slight regain also maintained a plateau for the remainder of the study.

The proportion of NB32-treated subjects who achieved ≥ 5% weight loss from baseline ranged from 44.5% (Study NB-304) to 66.4% (Study NB-302) (however only 39.5% with the NB16 dose in NB-301). Results were statistically significant ($p<0.001$) compared to the proportion of placebo-treated subjects (16.4% in Study NB-301 to 42.5% in Study NB-302).

The proportion of subjects who met the CHMP-recommended weight loss criterion of ≥ 10% weight loss, at the endpoint following NB32 treatment (18.5% to 41.5%, FAS, LOCF) was statistically superior compared with placebo (5.7% to 20.2%, FAS, LOCF). The range for the all-randomised set using BOCF was 13.4% to 30.3% for patients taking NB32 and 4.2% to 17.3% for patients on placebo.

The differences between NB32 and placebo for the responder analyses were lowest in patients with type 2 diabetes (Study NB-304).

It is conceivable that the patients who obtain a significant weight loss are the same as those who suffer from nausea (common adverse reaction with NB). However, the Applicant has provided reassurance that nausea was not a significant factor in causing the weight loss obtained with NB.

Because the drop-out rate in the studies was high (roughly 50% across the studies over one year), sensitivity analyses across multiple datasets and using different imputation methods for missing data as well as repeated measures mixed effect model approaches were important. These analyses gave results consistent with those of the primary analyses. The BOCF analyses were less convincing but may be considered to be the most realistic results on which to base a decision because they represent a comparison of randomised groups and impose a penalty for the high dropout rates. Alternatively, BOCF could be seen as a very conservative imputation method because it does not allocate any benefit to patients who discontinued prematurely and had a substantial weight loss at the time of discontinuation.

For the description of the study results in the SmPC, as noted above, the LOCF was maintained but using a more conservative analysis set (ITT dataset) for the mean weight loss results (with adherence rates included in the text). The BOCF was used for the responder analyses. Please refer to Tables 2 and 3 in section 5.1 of the SmPC.

The primary efficacy results were supported by favourable effects on a number of secondary efficacy variables such as change in excess body weight, waist circumference, blood lipids (mainly HDL-cholesterol and triglycerides) and hs-CRP. There were also notable favourable effects in glycaemic control, both in non-diabetics but particularly in patients with type 2 diabetes. However, the clinical significance of the changes in parameters measuring insulin resistance as well as progression to type 2 diabetes (in the studies including non-diabetics) is questionable.

With regard to quality of life (QoL), there were some positive findings in the huge of pool of IWQOL-Lite (the employed QoL scale) items and on the total score for three of the four studies. However, the differences in total score between NB and placebo were small and of doubtful clinical relevance. Therefore the CHMP did not agree to mention them in the SmPC.

The results on control of eating provided some support to the proposed mode of action. However, the results on food craving were inconclusive.

Baseline depressive symptomatology in the Phase 3 programme was scarce, and the results on depressive symptoms were inconclusive.

Subgroup analyses based on the pooled dataset indicated a relatively consistent efficacy across a wide range of demographic and baseline characteristics. A more pronounced weight reduction in females, in White patients and in patients with BMI <30 kg/m2 was however suggested. There were also suggestions of increased efficacy in patients without hypertension and without impaired glucose tolerance. The latter finding should be seen in the perspective that Study NB-304 indicated that the treatment effect of NB may be smaller in patients with type 2 diabetes than in non-diabetic patients. There was no treatment interaction by smoking status.

Overall, the efficacy results outlined and discussed above indicate a modest effect of NB32 but clinically relevant.

The efficacy of NB16 is less than that of NB32, and also in the context of the safety results, it is agreed that NB32 is the preferred and recommended dose.

One important exception from the overall favourable results of NB32 on secondary endpoints is the effect on blood pressure where NB32 consistently increased blood pressure when subtracting the effects in the placebo group. Initially, this was a significant concern and will be addressed further in the assessment of safety.

The Applicant proposed to include a recommendation in section 4.2 of the SmPC that patients should be evaluated after 16 weeks of treatment and that discontinuation of NB should be considered if a clinically meaningful weight loss (approximately 5%) is not present at that time. The rationale for this recommendation was initially questioned by the CHMP. Subsequently, the Applicant stated in its response that the 5% weight loss criterion at Week 16 is based on receiver operating characteristic (ROC) analyses of the pooled Phase 3 study data to calculate the sensitivity, specificity, and accuracy of combinations of various thresholds of early weight loss (2 to 5%) and early visits (Weeks 4 to 16). The rationale for recommending the 16 week threshold was retrospective Phase 3 analyses that indicated a strong relationship between early and later weight loss and suggested that the most appropriate threshold to support continued long-term treatment with NB32 was achieving at least 5% weight loss by Week 16. Those subjects not attaining that level of weight loss were less likely to achieve clinically meaningful weight loss with continued treatment.

The proposal to discontinue treatment after 16 weeks if patients have not lost at least 5% of their initial body weight is supported by the clinical data and was acceptable. Furthermore, the CHMP considered the need to reflect the stopping rule in the indication and include this sentence to section 4.1 of the SmPC.

The positive predictive values predict how many patients will achieve a relevant (≥ 5%) weight loss at the end of the treatment period, in this case 56 weeks. The positive predictive values for predicting the relevant response (≥ 5% weight loss) at 56 weeks were calculated for different time points: 12, 16 and 20 weeks. Based on the weight loss of ≥ 5% at 12, 16 and 20 weeks, the positive predictive values were 77.18%, 86.4% and 90.2%, respectively. The corresponding negative predictive values for 12, 16 and 20 weeks were 85.2%, 84.9% and 86.4%, respectively. Hence, a weight loss of >=5% at 16 weeks will predict a sustained weight loss at 56 weeks with a probability of approximately 85%. Thus, the choice of the 16-week time point appears reasonable and acceptable.

It is agreed that there seems to be no reason to mandate a maximum treatment duration. However, this need for on-going treatment should be factored in to the decision on the benefit-risk balance. Thus the need for continued treatment should be re-evaluated annually as mentioned in section 4.2 of the SmPC.

Apart from the dose-finding studies and the four pivotal studies presented and assessed above, additional Phase 2 studies provided supplemental, although very limited evidence. Study NB-431 was an fMRI study, which provided mechanistic insight and support for pursuing development of NB in management of weight. Studies NB-401 and NB-402 were exploratory open-label, uncontrolled studies in overweight/obese patients undergoing a smoking cessation programme and having major depression, respectively. No firm conclusion regarding efficacy can be drawn from these studies.

2.5.5. Conclusions on clinical efficacy

Overall, the efficacy results indicate a moderate effect of NB32 in weight management, which is considered to be clinically significant. The proposed stopping rule is now included in section 4.1 of the SmPC, and is likely to enhance the benefit by prompting the prescribing physician to discontinue NB at a relatively early time point in patients with a poor likelihood of obtaining a clinically meaningful weight loss after one year.

2.6. Clinical safety

Patient exposure

For the purpose of the safety evaluation, three datasets were analysed: The primary dataset, the overall dataset and the non-diabetic/diabetic dataset. These datasets include data from all randomised patients who were administered at least one tablet of study treatment and had at least one investigator contact/assessment at any time after the start of study treatment, regardless of whether or not they discontinued the study.

The Primary dataset includes safety data from the placebo controlled studies NB-201, NB-301, NB-302, NB-303, and NB-304.

Relative to the Primary Dataset, the Overall Dataset includes an additional 149 patients exposed to NB32 (from NB-401, NB-402, and NB-201 after reassignment) and 85 patients exposed to NB50 (from OT-101).

The diabetic dataset includes obese patients with type 2 diabetes (T2DM) from study NB-304.

In addition, a cardiovascular outcome trial (CVOT) and a Phase 3b study (NB-404) are ongoing. The objective of the CVOT study is to assess the occurrence of major adverse cardiovascular events (MACE) in overweight and obese patients with cardiovascular risk factors receiving NB FDC. NB-404 study is a randomised, open-label, clinical trial designed to provide additional information regarding the real world weight loss potential of NB in combination with a US commercially available

comprehensive lifestyle intervention programme, compared to usual care. Data from NB-CVOT and NB-404 studies are not integrated/pooled with Phase 3 data in the present application as both studies are ongoing.

The mean and median for baseline characteristics (i.e., age, height, weight, BMI) were similar across dose and treatment groups. Mean age and weight was 45 years and 100 kg. The majority of patients were female (~82%) and White (~77%) and ~17% were Black. In each dose and treatment group, a majority of patients were evenly distributed between the ≥30 to <35 kg/m^2 obesity class (37%) and the ≥35 to <40 kg/m^2 obesity class (36%), while approximately 25% of patients were in the ≥40 kg/m^2 obesity class; less than 3% of patients were in the <30 kg/m^2 obesity class. Approximately 60% of patients had complicated obesity, half had dyslipidaemia, and a third had impaired fasting glucose or hypertension. About 10% of patients in the Total NB and placebo groups had T2DM (10.3%, 11.2% respectively). About 10% of patients had a history of depression and 4% had a history of anxiety. The diabetes population were 10 years older, nearly half the patients were male and they weighted about 5% more than the non-diabetic population. Both hypertension and dyslipidemia were more frequently presented among diabetic patients as was the use of concomitant medications. In both the Primary and Overall Datasets, the percentage of patients taking at least one concomitant medication was similar across treatment and dose groups. The most common classes of concomitant medications were propionic acid derivatives, anilides, and multivitamins. In the Primary Dataset, the incidence of antihypertensive medication use was similar in the Total NB and placebo groups (incidence of hypertension was 25%). In the Diabetic and Nondiabetic Datasets, the percentage of patients taking at least one concomitant medication was higher in patients with diabetes compared with patients without diabetes. The incidence of use was higher in the diabetic group for medications used to treat hypertension, heart disease, and diabetes. About 5% of NB treated patients used opioids as concomitant medication even though it is contraindicated. Following further clarification about opiate use in the studies, it is concluded that the SmPC sufficiently addresses that concomitant use of opiates is not recommended and in some cases contraindicated.

Patient exposure

Overall, the safety database included sufficient number of patients exposed for 6 and 12 months to adequately describe the safety on NB. According to the ICH E1 guideline, 6 months treatment in 300-600 patients or 100 patients exposed in 1 year should be adequate to characterize the pattern of adverse drug events over time. The exposure to NB fulfilled this requirement as 1663 (51.3%) patients received ≥365 days of NB treatment. The mean (SD) exposure for total NB treatment, was 35.4 (23.7) weeks. 165 diabetes patients received NB treatment for more than 52 weeks, which is also adequate to characterise the safety in diabetes patients. Mean exposure for diabetes patients were 35.3 (24.3) weeks, which was comparable to the non-diabetes patients.

The majority (25-34%) of patients discontinuing treatment with NB did so in the first 8 weeks and overall, between 40 and 50% of the patients in the phase 3 studies discontinued the studies. More patients treated with NB discontinued due to adverse events (22.9% NB patients and 12% placebo patients) whereas more placebo patients discontinued the studies due to lack of efficacy (1.7% NB patients and 6.1% placebo patients).

Table 2.7.4-10 Summary of Disposition: Primary Dataset, Safety Analysis

Primary Dataset	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	NB48 (N=61) n (%)	Total NB (N=3239) n (%)
Completed Treatment	828 (54.7%)	322 (50.9%)	1401 (55.0%)	24 (39.3%)	1747 (53.9%)
Discontinued Treatment	687 (45.3%)	311 (49.1%)	1144 (45.0%)	37 (60.7%)	1492 (46.1%)
Most common reason for discontinuing treatment*					
Adverse event	182 (12.0%)	129 (20.4%)	604 (23.7%)	9 (14.8%)	742 (22.9%)
Lost to follow up	145 (9.6%)	77 (12.2%)	166 (6.5%)	15 (24.6%)	258 (8.0%)
Withdrew consent	192 (12.7%)	67 (10.6%)	202 (7.9%)	9 (14.8%)	278 (8.6%)
Insufficient weight loss	92 (6.1%)	14 (2.2%)	40 (1.6%)	0	54 (1.7%)

Data Source: Table ISS.P.2-1.1
*≥2% in any group

Adverse events

Adverse events in general

Treatment emergent adverse events (TEAEs), was defined as events that occurred or worsened on or after the date of first dose until 7 days after the last confirmed dose. All Serious AEs that occurred within 30 days after the last dose of study drug were reported. The following criteria were used to identify TEAEs:

- TEAEs: ≥5% incidence in the Total NB group (or the NB32 group in the Non-diabetic/Diabetic Datasets) and at least twice the incidence of the placebo group.
- Severe TEAEs (Primary Dataset only): ≥0.4% incidence in the Total NB group and at least twice the incidence of the placebo group.
- Severe TEAEs (Non-diabetic/Diabetic Datasets only): ≥1% incidence in the NB32 group and at least twice the incidence of the placebo group. Note: Due to the low incidence of severe events and the small Diabetic Dataset sample size, a cut-off of ≥1% in the NB32 group (at least 4 patients in the Diabetic Dataset) was used as opposed to the ≥0.4% incidence cut-off in the larger Primary Dataset.
- AEs leading to treatment discontinuation (Primary Dataset only): ≥0.5% incidence in the total NB Group and higher than the incidence of the placebo group.
- AEs leading to treatment discontinuation (Non-diabetic/Diabetic Datasets only): ≥1% incidence in any group.

The definitions on the severity of adverse events and serious adverse events are acceptable. The severity of each AE was classified as severe (incapacitating, with inability to work or perform normal daily activity), moderate (discomfort of sufficient severity to reduce or adversely affect normal activity), or mild (discomfort noted, but no disruption of normal daily activity). A serious adverse event (SAE) was defined as follows: any adverse experience occurring at any dose of study drugs that results in death, a life-threatening adverse drug experience, in-patient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In the double-blind treatment phase, 85.5% of NB treated patients compared to 75% of placebo treated patients reported a TEAE. 62.5% of NB treated patients compared to 37.2% placebo treated

patients reported TEAEs in the dose-escalation phase, whereas 60.9% of NB treated patients and 64.2% of placebo treated patients reported TEAEs in the maintenance phase.

A greater percentage of patients with diabetes experienced at least one TEAE during the double-blind treatment phase compared with patients without diabetes in both the NB32 (90.4% vs. 86.6%) and placebo (85.2% vs. 73.8%) groups. This result is not unexpected given the older age of the subject population and that baseline conditions such as hypertension and hyperlipidaemia and the use of concomitant medications are more frequent in patients with diabetes. The incidences of TEAEs in the NB32 group in both the Diabetic and Non-diabetic Datasets were higher compared with the corresponding placebo groups during the dose escalation phase, and similar or less during the maintenance phase.

Table 2.7.4-23 Common Treatment-Emergent Adverse Events (≥5% in Any Group):Nondiabetic and Diabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset		Diabetic Dataset	
MedDRA Preferred Term	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Subjects with any TEAE	**993 (73.8%)**	**1920 (86.8%)**	**144 (85.2%)**	**301 (90.4%)**
Nausea	90 (6.7%)	687 (31.1%)	12 (7.1%)	141 (42.3%)
Vomiting	38 (2.8%)	212 (9.6%)	6 (3.6%)	61 (18.3%)
Constipation	97 (7.2%)	430 (19.4%)	12 (7.1%)	59 (17.7%)
Diarrhoea	63 (4.7%)	128 (5.8%)	16 (9.5%)	52 (15.6%)
Headache	142 (10.5%)	401 (18.1%)	15 (8.9%)	46 (13.8%)
Dizziness	42 (3.1%)	213 (9.6%)	9 (5.3%)	39 (11.7%)
Insomnia	80 (5.9%)	196 (8.9%)	9 (5.3%)	37 (11.1%)
Hypertension	27 (2.0%)	49 (2.2%)	7 (4.1%)	33 (9.9%)
Nasopharyngitis	101 (7.5%)	152 (6.9%)	23 (13.6%)	28 (8.4%)
Upper respiratory tract infection	136 (10.1%)	182 (8.2%)	16 (9.5%)	26 (7.8%)
Hypoglycaemia	1 (<0.1%)	2 (<0.1%)	12 (7.1%)	25 (7.5%)
Tremor	6 (0.4%)	81 (3.7%)	4 (2.4%)	22 (6.6%)
Dry mouth	30 (2.2%)	184 (8.3%)	5 (3.0%)	21 (6.3%)
Anxiety	41 (3.0%)	90 (4.1%)	2 (1.2%)	18 (5.4%)
Abdominal pain upper	17 (1.3%)	71 (3.2%)	3 (1.8%)	17 (5.1%)
Sinusitis	80 (5.9%)	102 (4.6%)	14 (8.3%)	16 (4.8%)
Diabetes mellitus	4 (0.3%)	0	15 (8.9%)	15 (4.5%)
Pain in extremity	27 (2.0%)	51 (2.3%)	12 (7.1%)	13 (3.9%)
Back pain	59 (4.4%)	89 (4.0%)	9 (5.3%)	9 (2.7%)
Influenza	40 (3.0%)	78 (3.5%)	9 (5.3%)	9 (2.7%)
Oedema peripheral	10 (0.7%)	12 (0.5%)	10 (5.9%)	2 (0.6%)

Data Source: Table ISS.S.6.1-3.1 and NB-304 CSR Table 14.3-2A.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]).
Adverse events were coded using MedDRA 9.1 for Study NB-304 and MedDRA 12.0 for the Nondiabetic Dataset.
For the Diabetic Dataset, the preferred term diabetes mellitus denoted worsening of diabetes mellitus.

The system organ classes (SOC) mostly affected were Gastrointestinal Disorders, Nervous System Disorders and Infections and Infestations. The incidences within the common SOC categories, were generally higher in the NB group compared with the placebo group with the exception of Infections and Infestations; Musculoskeletal and Connective Tissue Disorders; Metabolism and Nutritional Disorders; and Respiratory, Thoracic and Mediastinal Disorders.

During the double-blind phase, the notable TEAEs (i.e., ≥5% incidence in the NB32 group and at least twice the incidence of the placebo group) in patients with diabetes were generally the same as those seen in patients without diabetes. However, the relative difference between the NB32 and placebo

groups for nausea, vomiting, and diarrhoea was greater in patients with diabetes compared with patients without diabetes.

In the non-diabetic dataset 11.8% and 6.4% of TEAEs in the NB and placebo group, respectively, were categorized as severe compared with 18.3% and 11.2% in the diabetic dataset for the NB and placebo group, respectively. No relevant differences in the occurrence of mild and moderate adverse events were seen between the diabetic and non-diabetic groups.

TEAEs related to study drug were judged by the investigator to be 64.4% in the NB group and 36.1% in the placebo group. The distribution among SOCs is similar as the total TEAEs with gastrointestinal-, nervous system- and psychiatric disorders as the most common TEAEs related to the study drug.

The common TEAEs with the strongest dose-relationship were nausea, vomiting, dizziness, hot flush and hyperhidrosis. Less common TEAEs such as feeling jittery and vision blurred may also be dose related and headache and anxiety appeared dose related only during the titration phase.

With regard to the common SOCs and common TEAEs, no unique SOCs or events were identified in the Overall Dataset subgroups compared to the Primary Dataset subgroups.

Adverse events by system organ class

Gastrointestinal, nervous system and psychiatric disorders

- Nausea

In the primary dataset, nausea was the most pronounced TEAE affecting 31.8% of NB treated patients compared to 6.7% of placebo patients in the double blind phase. 24.8% NB treated patients reported nausea during the dose escalation phase compared to 9.9% in the maintenance phase, indicating that nausea is most pronounced in the beginning of the treatment. Occurrence of nausea peaked within 4 weeks and resolved in most patients by 24 weeks. Nausea caused 6.3% of discontinuations in the dose-escalation phase and 5.5% discontinuations in the maintenance phase. No events were considered serious. Diabetes patients reported an even higher degree of nausea events (42.3% in the NB group and 7.1% in the placebo group) and a higher degree of severe nausea events.

- Constipation, vomiting, dizziness, dry mouth, headache and insomnia

The seven TEAEs (nausea, constipation, vomiting, dizziness, dry mouth, headache, and insomnia) are consistent with the AE profiles for the individual components of NB (bupropion and naltrexone). All seven TEAEs occurred by more than 5% and with a higher incidence than placebo in both diabetes and non-diabetes patients. Only for the category of dizziness, one event was reported as serious in the non-diabetes patients. Incidence of treatment discontinuations due to the seven TEAEs were less than <2% in NB treated patients compared to less than 0.5% in placebo treated patients.

Psychiatric disorders

- Suicidality

The FDA indicated that the single question on suicidality in the IDS-SR may not adequately capture the full spectrum of events that could potentially occur. It was recommended that a retrospective assessment tool of suicidality like the Columbia Classification Algorithm of Suicide Assessment (C-CASA) be used to assess adverse events that could represent suicidal events (behavior and ideation). A meta-analysis was conducted to evaluate NB dose combinations compared to placebo in 5 double-blind, randomized and placebo controlled clinical trials that enrolled obese patients, as well as overweight patients with comorbidities (dyslipidemia, hypertension, or T2DM).

Overall, 94.9% of NB patients and 95.3% of placebo patients had no event (Code 0, defined as absence of possibly suicide-related adverse events [PSRAEs]) as identified by key word text-string

search. There were 4 events of suicidal ideation or behavior during this study, one event (1/3239, <0.1%) in the NB treatment group compared to 3 events (3/1515, 0.2%) in the placebo treatment group. The remaining events were determined by adjudication to demonstrate no evidence of suicidality. Results from this meta-analysis showed no treatment difference in suicidal ideation or worse, measured by C-CASA methodology, as evidenced by the estimated odds ratio of 0.14 (95% CI: 0.00, 1.72). The findings were also homogenous across studies.

- Depression

Depression was of special interest because of historical concerns surrounding antidepressant treatment and suicidal ideation and behaviour. A detailed assessment of the risk of depression using standardised psychometric tools (IDS-SR) as well as the review of depression-related TEAEs did not reveal an increased risk of depression with NB treatment. Occurrence of depression was similar in the placebo and NB treated patients and discontinuations due to a psychiatric event were approximately 2.5% in both placebo and NB treated patients. This is consistent with the CPMP conclusions following the referral under Article 36 of Directive 2001/83/EC, which stated that there is no clinical reason for suspecting bupropion to be causally associated with depression or suicide (CPMP/27610/02).

- Sleep disorders

In the double-blind treatment phase, 10.8% of NB32 treated patients experienced sleep disorders (most commonly insomnia) compared to 7.1% in the placebo group and 8.8% in the NB16 group suggesting a dose-response relationship. The percentage of subjects initiating sedative/hypnotic during the study period or using sedatives/hypnotic at the end of study participation was comparable between the NB group and the placebo group indicating that the increased frequency of sleep disorders was not associated with an increase use of sedatives/hypnotics.

Table 2.7.4-31 Incidence of Treatment-Emergent Adverse Events for TME of Psychiatric Events: Primary Dataset, Double-Blind Treatment Phase

Psychiatric TME Subclass	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with any Psychiatric TME AE	**196 (12.9%)**	**86 (13.6%)**	**449 (17.6%)**	**541 (16.7%)**
Depression	52 (3.4%)	15 (2.4%)	75 (2.9%)	91 (2.8%)
Suicide/Self-injury[a]	3 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Sleep Disorders	107 (7.1%)	56 (8.8%)	290 (11.4%)	349 (10.8%)
Anxiety	67 (4.4%)	22 (3.5%)	168 (6.6%)	195 (6.0%)
Patients with any Psychiatric TME treatment-emergent SAE	**0**	**0**	**1 (<0.1%)**	**1 (<0.1%)**
Anxiety	0	0	1 (<0.1%)	1 (<0.1%)
Patients discontinued due to a Psychiatric TME AE	**40 (2.6%)**	**16 (2.5%)**	**71 (2.8%)**	**91 (2.8%)**
Depression	18 (1.2%)	8 (1.3%)	22 (0.9%)	30 (0.9%)
Suicide/Self-injury[a]	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Sleep Disorders	8 (0.5%)	7 (1.1%)	23 (0.9%)	31 (1.0%)
Anxiety	13 (0.9%)	2 (0.3%)	25 (1.0%)	30 (0.9%)

Data Source: Table 2.7.4-70, Table 2.7.4-71, Table 2.7.4-72

a. The only preferred term that occurred in this category was suicidal ideation.

TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase])

Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Cognitive disorders

Cognitive disorders (attention, memory impairment and language) occurred more often in NB treated patients (2.9%) than in placebo-treated patients (1.0%), and 0.8% of NB treated patients and 0.3% of placebo treated patients discontinued the study due to cognitive adverse events. None of the cognitive events were serious. A number of cognitive symptoms have been included in section 4.8 of the SmPC.

Seizures and convulsions

Bupropion is known to be associated with dose related increase in occurrence of seizures and 2 patients in the NB32 group experienced a serious seizure event leading to discontinuation. One patient had no prior history of seizure, the other patient had diabetes and hypoglycemia which were suggested to be the disposing factors leading to seizure.

Additional data on CNS adverse events from the ongoing CVOT study

In NB-CVOT 24% of subjects were on an antidepressant medication. The incidence of SAEs in the psychiatric class was low and comparable between treatment groups. Adverse events that were not classified as SAEs or as leading to study discontinuation were not captured, however it is noted that the incidence of psychiatric adverse events leading to study discontinuation was 3 times higher in NB32-treated patients than those on placebo, with anxiety and insomnia being the main causes. The majority of these events were of moderate severity, and were considered by investigators to be related to treatment.

Psychiatric Adverse Events Leading to Study Medication Discontinuation (NB-CVOT CSR: Interim Analysis 1, Table 30)

	Placebo (N=4450)		NB (N=4455)
System Organ Class / Preferred Term	**n (%)**		**n (%)**
Subjects Reporting at Least One Adverse Event Leading to Discontinuation of Study Medication	**326 (7.3%)**		**1134 (25.5%)**
Psychiatric Disorders	**38 (0.9%)**		**124 (2.8%)**
Insomnia	16 (0.4%)		30 (0.7%)
Anxiety	9 (0.2%)		26 (0.6%)
Depression	8 (0.2%)		5 (0.1%)
Hallucination	0		10 (0.2%)
Nervousness	0		8 (0.2%)
Confusional state	2 (<0.1%)		5 (0.1%)
Affect lability	3 (0.1%)		3 (0.1%)
Abnormal dreams	0		5 (0.1%)
Nightmare	2 (<0.1%)		3 (0.1%)
Disorientation	0		4 (0.1%)
Mood altered	0		3 (0.1%)
Hallucination, auditory	0		2 (<0.1%)
Hallucination, visual	0		2 (<0.1%)
Libido decreased	0		2 (<0.1%)
Panic attack	0		2 (<0.1%)
Sleep disorder	0		2 (<0.1%)

Others

Regarding adverse events from the muscles and joints, no differences was observed between NB and placebo treatment.

Adverse events concerning sexual dysfunction were more frequent in the NB treated group, although the incidence was low. Events were primarily classified as unspecified and very few patients discontinued the study due to sexual dysfunction.

Liver function and gallbladder

Adverse events related to potential hepatotoxicity were equally distributed among both the NB- and placebo treated patients. 40 (1.2%) in NB treated patients and 16 (1.1%) placebo patients. Most events were elevated transaminases. 22 NB treated patients had gallbladder-related AEs compared to 7 in the placebo group. Ten (0.3%) NB patients with gallbladder-related treatment emergent severe adverse events were hospitalized and underwent gallbladder surgery compared to 1 placebo patient. The higher incidence of gallbladder events in the NB treated patients may be related to loss of body weight. More NB-treated patients (7 of 35 with elevated transaminases) discontinued the study due to elevated transaminases compared to placebo (1 of 14 with elevated transaminases).

Vascular disorders

Blood pressure-related TEAEs (including hypertension) in both the NB32 and placebo groups were reported mostly by patients with baseline hypertension (baseline incidence was higher in diabetes patients), were not serious, infrequently led to treatment discontinuation, and required medication in approximately two-thirds of these patients. When applying the proposed stopping rule in the NB-CVOT study, by the first interim analysis 1.8% of all patients randomised to NB discontinued treatment at Week 16 due to sustained increased blood pressure (≥ 10 mmHg compared to baseline) alone. Another 2.5% discontinued due to a combination of sustained increased blood pressure (≥ 10 mmHg compared to baseline) and <2% weight loss.

Arrhythmia AEs occurred at a higher incidence in NB-treated patients (5.5%) than in placebo-treated patients (4.2%). The increase was largely due to palpitations (2.4% in the NB group and 0.9% in the placebo group). Palpitations were reported along with dizziness in 12 of 90 patients (10 NB patients and 2 placebo patients), but were not associated with syncope. The incidence of Atherosclerotic Disease events was similar between the Total NB and placebo groups (6.4% and 5.7%, respectively). SAEs were rare (0.2% Total NB, 0.4% placebo) and 0.6% of Total NB patients discontinued treatment for an Atherosclerotic Disease events compared to 0.9% of placebo. The rate ratio of treatment emergent ischaemic heart events in the NB32 group compared to the placebo group was 1.35 (95% CI: 0.42-4.31).

Major cardiovascular events (MACE) were recorded. The broad MACE included myocardial infarction (MI), CNS bleedings, cerebrovascular (CVA) accident and cardiovascular (CV) deaths. The custom MACE furthermore included revascularisation events as a proxy for CV events. Eight MACE events occurred in the clinical studies, 5 in the NB group (4 MI during the studies and one MI that occurred 36 days after the patient had discontinued study drug (discontinuation was due to gastroesophageal reflux syndrome) and 3 in the placebo group (one with coronary artery disease, one with angina pectoris (AP) and one with cerebrovascular event). In total, 6 patients were revascularised, 4 NB patients (the 3 MI patients and 1 patient with angina pectoris (AP) and 2 placebo treated patients (for AP). 2 NB treated patients with MI had diabetes and 2 placebo treated patients with AP and Stroke had diabetes. Results using the broad MACE definition (without revascularisation) showed a rate ratio of 1.42 (95% CI: 0.27-7.53) for total NB compared to placebo and a rate ratio of 1.55 (95% CI: 0.31-7.75) for the NB32 treated patients compared to placebo. Including revascularisation procedures in the MACE definition (custom MACE) the rate ratio was 0.75 (95% CI: 0.17-3.38) for total NB treatment compared to placebo and 0.84 (95% CI: 0.20-3.52) for the NB32 treated patients.

Table 2.7.4-29 Treatment-emergent MACE Assessment: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)	NB32 (N=2545)		Total NB (N=3239)	
	Incidence, n (%)	Incidence, n (%)	Relative Risk (95% CI)[a]	Incidence, n (%)	Relative Risk (95% CI)[a]
Ischaemic heart disease SMQ	4 (0.26)	9 (0.35)	1.35 (0.42, 4.31)	9 (0.28)	1.28 (0.39, 4.20)
Broad MACE SMQ	2 (0.13)	5 (0.20)	1.55 (0.31, 7.75)	5 (0.15)	1.42 (0.27, 7.53)
Custom MACE+ revascularisation	3 (0.20)	4 (0.16)	0.84 (0.20, 3.52)	4 (0.12)	0.75 (0.17, 3.38)
Custom MACE	1 (0.07)	3 (0.12)	1.95 (0.22, 17.29)	3 (0.09)	1.69 (0.17, 17.06)
Nonfatal myocardial infarction[b]	0	2 (0.08)		2 (0.06)	
Cardiovascular death	0	1 (0.04)		1 (0.03)	
Stroke	1 (<0.1)	0		0	
Retrospectively Adjudicated MACE	4 (0.26)	3 (0.12)	NA	3 (0.09)	NA

Data Source:, Table 2.7.4-66; Table 2.7.4-67; Table 2.7.4-68; Table 2.7.4-69; M5.3.5.3, ISS table P.6.1-3.1; M5.3.5.3, Summary Document for Orexigen Cardiovascular Event Adjudication

a. RR and CI are calculated using the exact method and stratified by study.
b. One additional nonfatal myocardial infarction occurred >30 days post discontinuation of study in a subject who received NB16 during the treatment phase.
c. Retrospective adjudication (Duke), custom MACE + unstable angina includes 3 placebo subjects with unstable angina not previously identified.

Note: MACE definitions per previous FDA evaluations; Relative risk is exposure adjusted.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment.

A retrospective analysis from an independent adjudication committee yielded the same results regarding MACE and they found 4 additional cases of unstable AP in the placebo group. Even though the numbers are very small, the number of MI events was higher in the NB treated group compared to the placebo group and the data suggest that an increase in MACE might be an issue in these patients where many have additional risk factors such as hypertension. This was of major concern to the CHMP also in the context of the increase in blood pressure seen in the NB treated patients compared to placebo. A long-term safety outcomes study was requested by the FDA (NB-CVOT Light trial) to assess the occurrence of MACE with NB treatment versus placebo in patients at increased CV risk of adverse CV outcomes (pre-existing CV disease and/or diabetes) and is ongoing.

The Applicant has submitted the first interim report of the NB-CVOT study. The primary objective of the study is to assess NB compared to placebo with regard to the occurrence of MACE, defined as CV death, nonfatal myocardial infarction (MI), or nonfatal stroke in overweight and obese subjects.

At time of the interim analysis, 8910 subjects were randomised, and 8905 subjects were included in the ITT population; 4450 subjects in the placebo group and 4455 in the NB group. There was no notable difference in baseline characteristics as presented by the Applicant. Overall, the study included a sufficient amount of subjects with CV disease and CV risk factors. Accordingly, the majority of subjects were in concomitant treatment with antihypertensives, lipid altering medication and/or antidiabetic medication. Mean duration of drug exposure was 26.8 weeks for the placebo group and 30.5 weeks for the NB group. At the time of the interim analysis, 1201 (27.0%) and 2746 (38.3%) subjects in the placebo and NB treatment group respectively, were still treated with study medication. The discontinuation rate was higher than seen in the phase III studies, which may be due to the study design (at Week 16 discontinuation of subjects with lack of response [defined as <2% weight loss compared to baseline] or sustained increased blood pressure [defined as ≥ 10 mmHg compared to baseline]). This time of evaluation (16 weeks) is in accordance with the recommendations given in the proposed SmPC.

The primary analysis of the ITT population shows that statistically significantly more subjects treated with placebo (59 subjects, 1.3%) compared to NB (35 subjects, 0.8%) experienced MACE; hazard ratio (HR) (95%CI): 0.59 (0.39-0.90), p<0.0001. Furthermore, the secondary analysis of the PP population (referred to as on-treatment data) showed no difference between the placebo and the NB treatment groups. 27 (0.6%) and 23 (0.5%) MACE events in the placebo- and NB group respectively; HR (95%CI): 0.79 (0.45-1.38), p=0.0006. Nonetheless, in both populations, the confidence interval for the hazard ratio was less than 2, which was defined as the non-inferiority margin in this interim analysis. MACE was not correlated with weight loss, neither as categorical (</≥2% weight loss from baseline) nor as continuous measure. Likewise, no correlation was observed between MACE and blood pressure/ heart rate.

Overall, the results from the present interim analysis of the NB-CVOT study are reassuring and do not indicate an increased risk of CV disease in the short and intermediate-term.

Serious adverse events and deaths

In all, one death was reported in the study period. The death of a 65-year old male, treated with NB32, was judged as unrelated to study drug. The patient had comorbidities as hypercholesterolemia, hypertension, and bradychardia and experienced a fatal acute myocardial infarction on day 324 of study drug treatment.

During the double-blind treatment phase, of the 3239 patients treated with NB and 1515 patients treated with placebo, 74 and 25 patients experienced a serious adverse event (SAE). Of those 9 and 1 SEAs were in the dose escalation phase and 65 and 24 were in the maintenance phase. Of the 74 patients with a SAE in the Total NB group, 67 had SAEs considered unrelated to the study treatment. Of the 25 patients with a SAE in the placebo group, 24 had SAEs considered unrelated to the study treatment.

Treatment-emergent SAEs were reported in a higher percentage of patients in the NB32 group compared with the NB16 group (2.5% vs. 1.6%, respectively). No SAE term was reported for more than one patient in the NB16 group, and no SAEs were reported in the NB48 group.

The most common SAEs were gallbladder related and all these patients (10 [0.3%] NB patients and 1 placebo patient) were hospitalised and underwent gallbladder surgery. No differences were found in gallbladder events between NB and placebo treated patients as a function of demographic subgroup, disease history or concomitant medications.

Three NB treated patients in the double-blind treatment phase reported adverse events from the SOC of renal and urinary disorders, of those 2 were calculus ureteric.

During the double-blind treatment period, 16 patients in the NB treated group had SAEs related to SOC infections and infestations compared to 4 placebo treated patients. 3 NB treated patients experienced an acute myocardial infarction compared to 0 in the placebo group. In contrast to this finding, angina pectoris and atrial fibrillation occurred in 4 placebo treated patients (2 each diagnosis) and in 0 NB treated patients.

Apart from 2 diabetes patients experiencing vasovagal syncope, the serious adverse events in the diabetic population were similar to the non-diabetic population for the SAEs occurring ≥2 patients.

Table 2.7.4-24 Incidence of Treatment-Emergent Serious Adverse Events Occurring in ≥2 Subjects in Any Group: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

Preferred Term	Nondiabetic Dataset		Diabetic Dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Subjects with any SAE	**17 (1.3%)**	**51 (2.3%)**	**8 (4.7%)**	**13 (3.9%)**
Syncope vasovagal	0	0	0	2 (0.6%)
Cellulitis	1 (<0.1%)	2 (<0.1%)	1 (0.6%)	1 (0.3%)
Cholecystitis	1 (<0.1%)	5 (0.2%)	0	1 (0.3%)
Myocardial infarction	0	2 (<0.1%)	0	1 (0.3%)
Staphylococcal infection	0	2 (<0.1%)	1 (0.6%)	0
Calculus ureteric	0	2 (<0.1%)	1 (0.6%)	0
Non-cardiac chest pain	1 (<0.1%)	2 (<0.1%)	0	0
Angina pectoris	0	0	2 (1.2%)	0
Atrial fibrillation	0	0	2 (1.2%)	0
Dehydration	0	2 (<0.1%)	0	0

Data Source: Table ISS.S.6.2-3.1 and NB-304 CSR Table 14.3-13A
Treatment-emergent SAEs were defined as SAEs that first occurred or worsened during the double-blind treatment phase (first dose date ≤ adverse event onset date ≤ last confirmed dose date + 7 days, excluding adverse events that occurred during the drug discontinuation or extension phase).
Adverse events were coded using MedDRA 9.1 for Study NB-304 and MedDRA 12.0 for the Nondiabetic Dataset.

Laboratory findings

Vital Signs, Physical Findings, and Other Observations Related to Safety

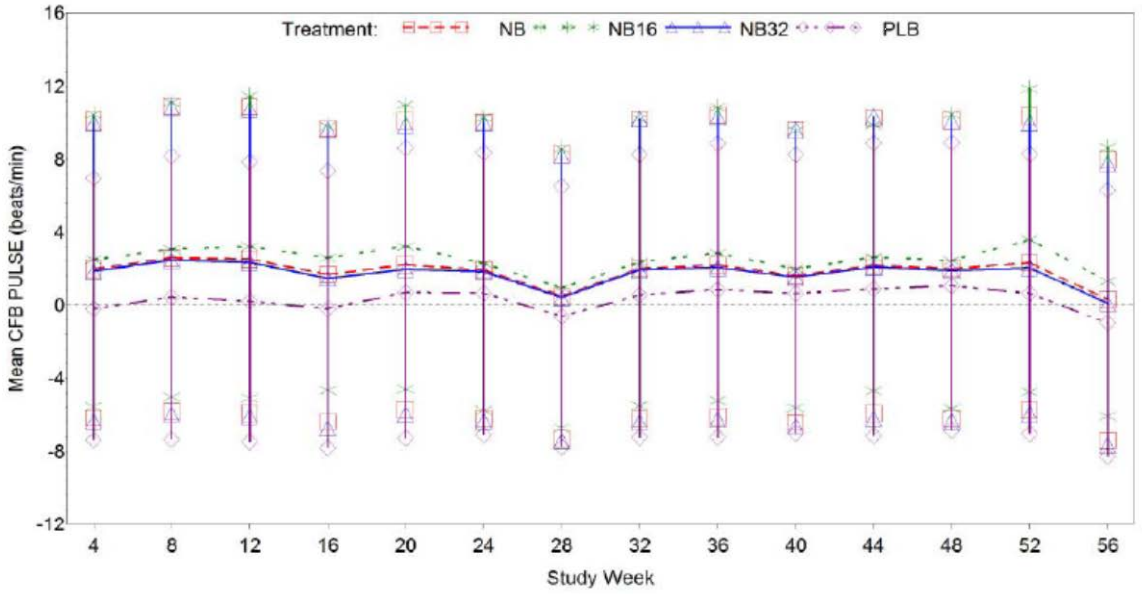
Heart rate and blood pressure

Heart rate and blood pressure were measured after 5 minutes in sitting position at every study visit, the average value was reported.

- Heart rate

Across monthly time points, mean heart rate in the placebo group generally fluctuated from baseline by ±1 bpm, while mean heart rate in the Total NB group from Week 4 through Week 56 tended to increase by approximately 2 bpm (range: 0.30 bpm to 2.58 bpm) above baseline with no apparent pattern over time.

Figure 2.7.4-2 Mean Change (± SD) from Baseline in Heart rate by Study Visit; Primary Dataset, Double-Blind Treatment Phase



Data Source: Figure ISS.P.2-3.
Abbreviations: CFB=change from baseline; NB=all doses of combination naltrexone and bupropion treatment

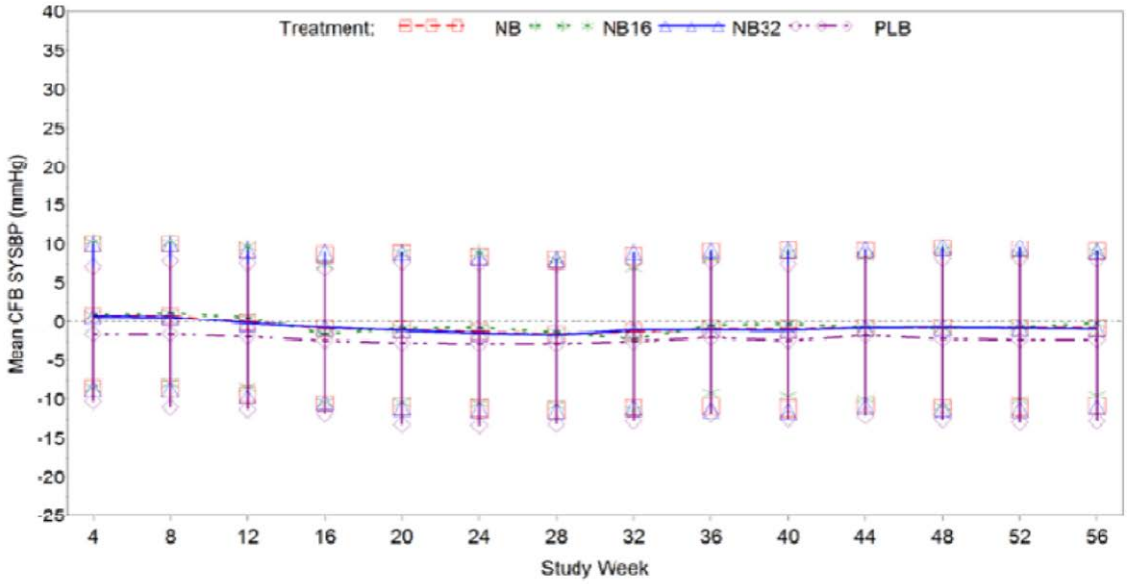
The mean change in heart rate from baseline to endpoint was ±1 beats per minute (bpm) in both groups. The maximum pulse was 126 bpm in the NB group and 114 bpm in the placebo group.

More NB treated patients' experienced treatment-emergent increases of 5, 10 and 20 bpm over baseline in heart rate during the double-blind treatment phase.

- Blood pressure

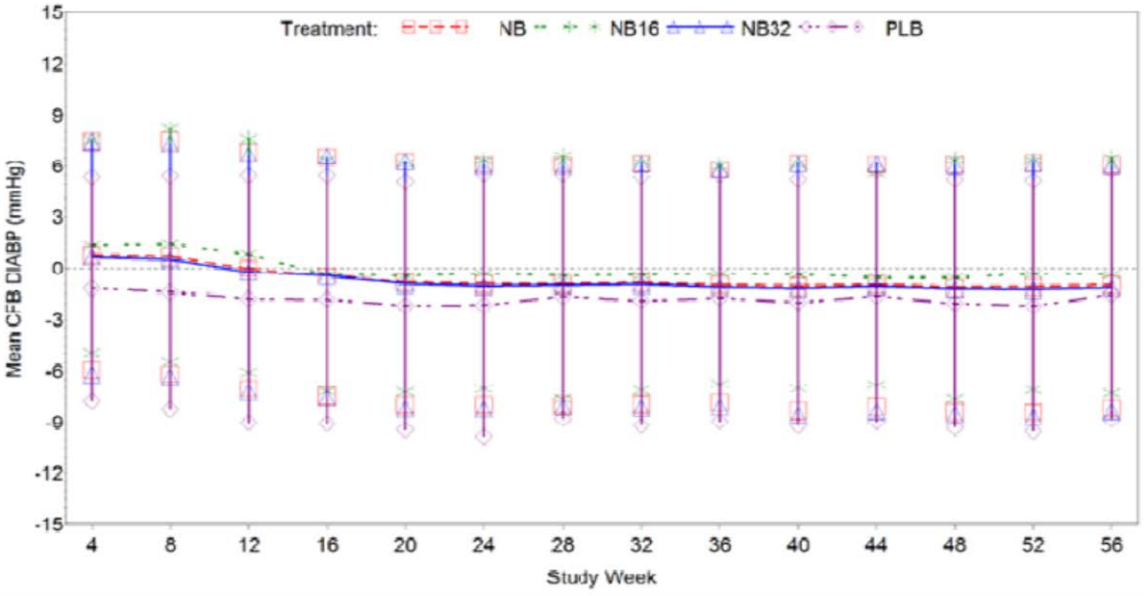
The mean decrease from baseline to endpoint in SBP was 0.28 mmHg in the NB group and 1.64 mmHg in the placebo group. Mean decrease from baseline to endpoint in DBP was 0.53 in the NB group and 1.27 in the placebo group.

Figure 2.7.4-3 Mean Change (± SD) from Baseline in SBP by Study Visit: Primary Dataset, Double-Blind Treatment Phase



Data Source: Figure ISS.P.2.2-1.
Abbreviations: CFB=change from baseline; NB=all doses of combination naltrexone and bupropion treatment including NB48; SYSBP=systolic blood pressure.

Figure 2.7.4-4 Mean Change (± SD) from Baseline in DBP by Study Visit: Primary Dataset, Double-Blind Treatment Phase



Data Source: Figure ISS.P.2.1-1.
Abbreviations: CFB=change from baseline; DIABP=diastolic blood pressure; NB=all doses of combination naltrexone and bupropion treatment including NB48

The difference in SBP for NB compared to placebo at week 4 was 2.39 mm Hg (95% CI: 1.85-2.94) and at week 52 it was 1.52 mm Hg (95% CI: 0.71-2.33). For DBP the difference compared to placebo at week 4 was 1.9 mm Hg (95% CI: 1.51-2.28) and at week 52 it was 1.08 mm Hg (95% CI: 0.52-1.64).

More NB treated patients compared to placebo patients had values of BP above 160/100 mmHg as well as increases of 10, 15 and 20 mmHg over baseline values of blood pressure.

The mean change from baseline to maximum SBP was approximately 7 mm Hg (placebo) to 9 mm Hg (Total NB) and the mean change from baseline to maximum in DBP was approximately 5 mm Hg (placebo) to 6 mm Hg (Total NB).

Table 4-16 Change from Baseline to Endpoint and to Maximum in Systolic Blood Pressure: Primary Dataset, Double-Blind Treatment Phase

mm Hg	Placebo (N=1419)		Total NB (N=2812)	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**
Mean ± SD	119.10±10.39	117.46±11.35	118.96±10.35	118.68±11.82
Mean Change from BL ± SD	--	-1.64±9.95	--	-0.28±10.07
Minimum	85.00	81.00	85.00	85.00
Maximum	145.00	165.00	148.00	172.00
	Baseline	**Maximum***	**Baseline**	**Maximum***
Mean ± SD	119.10±10.39	126.30±11.64	118.96±10.35	127.47±12.02
Mean Change from BL ± SD	--	7.20±9.40	--	8.52±9.95
Minimum	85.00	91.00	85.00	89.00
Maximum	145.00	203.00	148.00	184.00

Data Source: Tables ISS.P.8.2-1 and ISS.P.8.2-3.
N represents total number of subjects with postbaseline measurements.
* Results are based on the maximum value observed within 7 days of last confirmed dose.
Abbreviations: BL=baseline; SD=standard deviation; Total NB=all doses of combination naltrexone and bupropion treatment.

Table 4-27 Change from Baseline to Endpoint and to Maximum in Diastolic Blood Pressure: Primary Dataset, Double-Blind Treatment Phase

mm Hg	Placebo (N=1419)		Total NB (N=2812)	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**
Mean ± SD	77.07±6.93	75.80±7.71	76.98±7.23	76.45±7.82
Mean Change from BL ± SD	--	-1.27±7.31	--	-0.53±7.19
Minimum	52.00	42.00	46.00	50.00
Maximum	95.00	109.00	97.00	105.00
	Baseline	**Maximum***	**Baseline**	**Maximum***
Mean ± SD	77.07±6.93	81.89±7.00	76.98±7.23	82.87±7.50
Mean Change from BL ± SD	--	4.82±6.49	--	5.89±6.75
Minimum	52.00	57.00	46.00	56.00
Maximum	95.00	109.00	97.00	121.00

Data Source: Tables ISS.P.8.1-1 and ISS.P.8.1-3.
N represents total number of subjects with postbaseline measurements.
* Results are based on the maximum value observed within 7 days of last confirmed dose.
Abbreviations: BL=baseline; SD=standard deviation; Total NB=all doses of combination naltrexone and bupropion treatment.

- Heart rate and blood pressure by weight loss category and by diabetes status

Mean changes in SBP, DBP and heart rate from baseline to week 56 endpoint (FAS) according to weight loss category (no change/gain, >0-<5%, ≥5%-<10% and ≥10%) were evaluated. The NB treated patients in the weight loss category no change/gain and >0-<5%, experienced increases in SBP and DBP. Decreases in SBP and DBP were seen for weight loss category ≥5%-<10% and ≥10% only, whereas the placebo treated patients had decreases in SBP and DBP regardless of weight loss category.

Treatment with NB yielded less decreases in SBP and DBP in the weight loss categories ≥5%-<10% and ≥10% compared to placebo. In the weight loss category ≥5%-<10%, the SBP and DBP decreased with 0.5 mmHg and 0.6 mmHg, respectively, in the NB treated patients compared to 3.6 mmHg and 3.0 mmHg in the placebo patients. In the weight loss category ≥10% the decreases in SBP and DBP were 2.1 mmHg and 2.2 mmHg in NB treated patients compared to 6.1 mmHg (SBP) and 4.0 mmHg (DBP) in placebo treated patients. Heart rate decreases in the NB treated patients were seen in the weight loss category ≥10% only (0.3 bpm for NB patients and 2.9 in placebo patients).

Incidences of treatment emergent increases in heart rate were comparable between diabetes and non-diabetes patients treated with NB indicating that diabetes patients did not react more to NB than non-diabetes patients regarding heart rate. Placebo treated diabetes patients had higher incidences of heart rate increases than placebo treated non-diabetics.

Patients with diabetes had more often treatment-emergent increases in both SBP and DBP compared to patients with no diabetes and these differences were present in both the NB treated and placebo treated patients, indicating that diabetes patients are more prone to increases in blood pressure, although it seems to be independent of NB treatment.

- 24-hour ambulatory blood pressure

In the sub study from NB-303, comparison of the means of average daytime and nighttime systolic and diastolic blood pressures showed that normal circadian rhythm was maintained for both the NB and placebo groups.

The mean daytime SBP and DBP decreased by 2.7 mmHg and 1.6 mmHg in the placebo group whereas both SBP and DBP increased by 0.16 and 1.15, respectively, in the NB treated group of patients. During nighttime, mean SBP and DBP in both the NB and placebo group decreased although the decrease was smaller in the NB treated group. Also the mean maximum blood pressures were much higher in the NB group compared to the placebo group, whereas the minimum BP values were more similar (table 2.7.4-53). It seems that NB treated patients are more prone to high blood pressure increases than placebo patients. Applying the proposed stopping rule with evaluation at Week 16 should ensure that treatment with NB is not continued in patients with concerns with the safety and tolerability of ongoing treatment. The need to discontinue treatment if increased blood pressure is included in the warning section of the SmPC.

Table 2.7.4-53 Average Daytime and Night-time ABPM Systolic and Diastolic Blood Pressure (mm Hg) Mean Change from Baseline to Endpoint: ABPM Substudy Analysis Set (Study NB-303 ABPM)

	Baseline		Endpoint		Change from Baseline	
	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum
Daytime Systolic Blood Pressure						
Placebo (N=38)	126.36 (10.34)	105.34, 152.07	123.66 (10.92)	106.45, 147.61	-2.71 (8.26)	-21.31, 17.37
NB32/48 (N=79)	126.02 (9.12)	108.72, 147.04	126.17 (10.62)	97.82, 151.65	0.16 (7.68)	-20.82, 24.98
Daytime Diastolic Blood Pressure						
Placebo (N=38)	77.70 (8.94)	58.90, 95.07	76.07 (7.68)	63.00, 89.98	-1.63 (5.38)	-14.03, 7.86
NB32/48 (N=79)	77.92 (7.38)	60.10, 92.75	79.07 (8.37)	52.31, 102.07	1.15 (5.94)	-16.47, 22.76
Night-time Systolic Blood Pressure						
Placebo (N=38)	114.33 (9.10)	97.92, 138.48	112.19 (10.38)	93.89, 132.85	-2.15 (7.47)	-25.07, 10.52
NB32/48 (N=79)	112.92 (10.64)	93.86, 149.35	111.39 (10.76)	88.74, 135.65	-1.53 (9.19)	-23.98, 23.65
Night-time Diastolic Blood Pressure						
Placebo (N=38)	65.90 (7.67)	51.96, 78.92	63.73 (8.20)	51.64, 79.04	-2.18 (4.68)	-12.00, 5.24
NB32/48 (N=79)	64.25 (8.04)	48.48, 86.00	64.14 (7.32)	49.20, 84.44	-0.11 (7.03)	-15.82, 17.13

Source: NB-303 ABPM Sub-Study CSR Table 10.
Sub-study analysis set includes all subjects who were randomised in the sub-study, had a baseline ABPM measurement, were administered at least one tablet of study treatment, and had at least one investigator contact/assessment after the start of study treatment.
Abbreviations: NB32/48 = pooled group of subjects received either naltrexone PR 32 mg/bupropion PR 360 mg or naltrexone PR 48 mg/bupropion PR 360 mg

ECG

In the NB clinical trials, there was no evidence of treatment-related QTc prolongation in NB-treated patients compared with placebo. Cardiac arrhythmias were uncommon in NB clinical trials and no instances of life-threatening arrhythmias were reported. Neither naltrexone nor bupropion alone are reported to prolong the QTc interval or cause rapidly activating delayed rectifier K+ current (iKr) blockade.

Review of ECG reports in the Diabetic dataset indicated no changes from baseline across the treatment groups and no difference between groups, especially with respect to changes in QTc, occurrence of ECG-related serious or non-serious TEAEs, or in individual clinically significant ECG findings.

Haematology and Chemistry

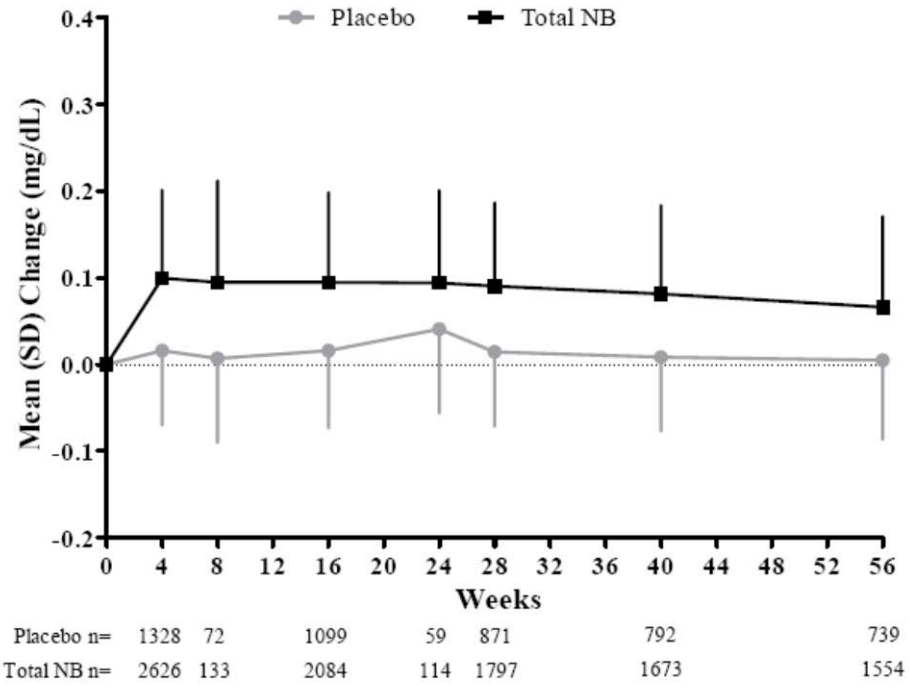
Haematology

Mean values for haematology samples for all dose groups, including Total NB, individual doses, and placebo, were within the normal range at baseline and at endpoint in the Primary Dataset. 7.3% of NB treated patients experienced a shift to low lymphocyte values compared to 3.7% in the placebo group. Three patients in the total NB group discontinued the study due to abnormal laboratory findings (decreased haematocrit and leukopenia) and two of them were considered to be drug related, however not serious.

Chemistry

Increased mean serum creatinine throughout the study period were seen for NB treated patients (both NB16 and NB32), although a small reduction in serum creatinine at week 56 relative to week 4 was seen. 2 patients had a single serum creatinine measurement above 2 mg/dl (normal range 0.5-1 mg/dl in females, 0.7-1.2 mg/dl in males). One patient continued the study as all other measurements were normal. The other patient had 3 measurements above ULN which returned to normal afterwards. The patient discontinued due to lack of efficacy. No changes in creatinine in the placebo group were observed. Bupropion and its metabolites inhibit the organic cation transporter 2 (OCT2) in the basolateral membrane in the renal tubules, and that could be an explanation for the increased creatinine during study treatment. Blood urea nitrogen (BUN) was unchanged in both NB and placebo groups.

Figure 2.7.4-1 Creatinine, Mean change from Baseline by Visit: Primary Dataset, Double-Blind Treatment Phase



Data Source: Table ISS.P.REN.6-1
Results are based on observed values.

For patients with diabetes compared with patients without diabetes shifts to high creatinine occurred at a higher incidence in the NB32 group compared with the placebo group for both the Diabetic (12.7% and 3.1%, respectively) and Non-diabetic Datasets (7.5% and 1.7%, respectively). This was addressed in the D120 list of questions. The Applicant explained that no difference in mean placebo-corrected increase in creatinine from baseline to endpoint was observed between subjects with/without DM and reassuringly, concomitant use of metformin did not affect changes in creatinine. The explanation for the observation is probably that the group of DM subjects had a higher baseline creatinine compared to the group of subjects without DM. This is considered a plausible explanation and in clinical practice, it is not expected to pose a major safety concern. In section 4.4 of the SmPC, it is recommended to assess estimated glomerular filtration rate (eGFR) prior to initiating therapy with naltrexone / bupropion in individuals who are at elevated risk for renal impairment (including but not limited to patients with diabetes).

Safety in special populations

Elderly

In the primary dataset, higher incidences of dizziness, tremor and hypertension were noted in NB patients ≥65 years old compared to younger NB patients (age categories 18-44 and 45-64 years old). These events rarely resulted in study discontinuation. The small number of patients in the ≥65 year old group (n=62, Primary Dataset) and overrepresentation of patients with diabetes in this age group makes it difficult to draw definitive conclusions.

Additional data are available from Study NB-CVOT in subjects ≥ 65 years of age (Table 151-1). These confirm that the incidence of adverse events increases with age. Among subjects ≥65–<75 years, 32.5% in the NB group experienced an AELDSM compared to 9.2% in the placebo group. For subjects ≥75 years, 45.5% and 8.1% in the NB and placebo group respectively, experienced an AELDSM. Also the percentage of serious adverse events increased with age, and 12.3% of all subjects aged ≥75 years and treated with NB experienced a serious adverse event. Based on these results, the Applicant has agreed to include information regarding the elderly in section 4.2 of the SmPC. Subjects aged ≥65–<75 years should be treated with caution and use of NB in patients ≥75 years is not recommended.

Table 151-1: Incidence of AELDSM in Study NB-CVOT Subjects Overall Versus Subjects 65 Years or Greater in Age: ITT Population (Study NB-CVOT, Interim Analysis 1)

AELDSM	Overall		Subjects ≥65 years	
	NB (N=4455)	Placebo (N=4450)	NB (n=1482)	Placebo (n=1397)
Overall	25.5%	7.3%	33.9%	9.1%
AELDSM ≥1% incidence				
Nausea	7.4%	0.4%	9.1%	0.4%
Constipation	2.6%	0.3%	4.5%	0.6%
Vomiting	2.0%	<0.1%	2.4%	0.1%
Tremor	1.7%	0%	2.9%	0%
Dizziness	1.5%	0.1%	2.2%	0%
Headache	1.2%	0.3%	1.4%	0.4%

Patients with diabetes

Type 1 DM was an exclusion criterion in the clinical studies but Trial NB-304 included patients with T2DM. Thus, NB treatment was evaluated in 333 T2DM patients and the findings in this patient group are discussed in the different sections of this discussion on clinical safety.

The CVOT study also included a substantial number of patients with diabetes. Based on these data, only few subjects reduced the dose or discontinued metformin treatment with no noticeable difference between treatment groups. Concomitant use of NB and metformin is not expected to pose problems.

Patients with renal impairment

Please also refer to section on pharmacokinetics.

27% of subjects in Study NB-CVOT (interim results) had renal impairment (eGFR <90 mL/min) at screening with 15% of these subjects (n=348) classified as having moderate renal impairment (eGFR 30 to 59 mL/min). While incidences on placebo are similar, there is a clear pattern of more adverse events leading to study discontinuation in patients with renal impairment than in patients with normal renal function in the NB group.

AELDSM	Overall		Subjects with Renal Impairment	
	NB (N=4455)	Placebo (N=4450)	NB (n=1220)	Placebo (n=1174)
Overall	25.5%	7.3%	32.9%	7.8%
AELDSM ≥1% incidence				
Nausea	7.4%	0.4%	10.3%	0.3%
Constipation	2.6%	0.3%	3.3%	0.4%
Vomiting	2.0%	<0.1%	3.0%	0.1%
Tremor	1.7%	0%	2.1%	0%
Dizziness	1.5%	0.1%	2.0%	0%
Headache	1.2%	0.3%	1.0%	0.4%
Diarrhoea	0.8%	0.4%	1.0%	0.6%

Patients with hepatic impairment

NB was not investigated in patients with hepatic impairment. Please also refer to the section on pharmacokinetics.

Pregnancy and lactation

In the Primary dataset (women only) there were 20 (0.74%) pregnancies with at least 7 days of foetal exposure in the NB group resulting in 10 normal babies and 6 (0.48%) pregnancies in the placebo group resulting in 5 normal babies. No congenital abnormalities were observed. 4 of the 20 pregnancies resulted in 4 spontaneous miscarriages and 3 of 20 in elective terminations in the NB group compared to 0 in the placebo group. Bupropion, naltrexone and their metabolites are excreted in breast milk. NB should not be used in pregnant women, women intending to become pregnant and lactating women.

Safety related to drug-drug interactions and other interactions, overdose, abuse and ability to drive/operate machinery

Please refer to section on pharmacokinetics and pharmacodynamics for drug-drug interactions.

Potential for interaction between the sustained release drug product and alcohol is an important safety consideration. In vitro dissolution testing of naltrexone and bupropion from NB tablets at varying alcohol concentrations demonstrated that drug release does not exceed release rates into standard aqueous media. Therefore, there is no concern of acute release of drug when NB tablets are ingested in the presence of alcohol.

No events of overdose were observed in the NB clinical programme. Overdose with bupropion as monotherapy has been reported and seizures were reported in one third of cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. There is no clinical experience with naltrexone overdose.

There were no deaths or SAEs attributable to drug abuse or withdrawal, no overdoses, and no evidence of drug diversion or inappropriate self-administration with NB in the clinical development programme.

There was no indication of a discontinuation-emergent withdrawal syndrome in the integrated safety analysis. Examination of safety data from the NB clinical development programme shows that NB does affect cognitive ability (see previous sections). The incidence of injuries was similar between NB-treated patients and placebo-treated patients.

Discontinuation due to adverse events

The majority of discontinuations due to adverse events happened in the dose-escalation phase, where 17.4% of the NB treated patients discontinued the study compared to 4.4% placebo treated patients. The most common adverse event leading to discontinuation (i.e., adverse events occurring at a ≥1.0% incidence in the Total NB group and higher than the incidence of the placebo group) in the dose-escalating phase in NB treated patients was nausea (5.5% of NB patients, <0.1% [1 patient] of placebo patients).

During the whole double-blind treatment phase, 23.8% of the NB treated patients discontinued the study due to an adverse event, again nausea was the most frequently reason to discontinue the study in the NB treated patients. In placebo treated patients 11.9% discontinued the study due to an adverse event. The percentages of patients discontinuing after the dose-escalation phase is similar in the NB and placebo group (6.4% in NB group and 7.5% in the placebo group). There were no patterns in the adverse events in the placebo group. In general, the incidence of discontinuations due to an adverse event was similar among NB dose groups, although in the Overall dataset a dose-response relationship for the incidence of nausea is suggested: 5.1% for NB16, 6.2% for NB32 and 13% for NB48/NB50.

In the analyses of adverse events leading to discontinuation by baseline characteristics and a ≥5% weight loss at endpoint, the overall incidence of adverse events leading to discontinuation was higher for females, Hispanics, and non-smokers in the Total NB group compared with males, non-Hispanics and smokers, respectively; in the placebo group, incidences were similar between these subgroups. These differences were judged as not clinically relevant.

Patients with diabetes, discontinued the study more than non-diabetic patients in both the NB group and placebo group. Nausea was more pronounced in the diabetes population, and almost 10% discontinued the study because of nausea. Concomitant treatment with metformin might be a contributing factor but in general, few patients had their NB dose reduced or discontinued metformin. Overall, concomitant treatment with metformin and NB does not warrant precautions.

Table 2.7.4-25 Most Common (≥1% in Any Group) Adverse Events Resulting in Treatment Discontinuation: Nondiabetic and Diabetic Datasets, Double-Blind Treatment Phase and Dose-Escalation Phase

MedDRA Preferred Term	Nondiabetic Dataset		Diabetic Dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Double-Blind Treatment Phase				
Subjects discontinuing treatment due to any AE	**156 (11.6%)**	**514 (23.2%)**	**26 (15.4%)**	**98 (29.4%)**
Nausea	3 (0.2%)	128 (5.8%)	0	32 (9.6%)
Vomiting	1 (<0.1%)	18 (0.8%)	0	10 (3.0%)
Headache	9 (0.7%)	37 (1.7%)	0	6 (1.8%)
Depression	10 (0.7%)	8 (0.4%)	3 (1.8%)	2 (0.6%)
Diabetes mellitus	2 (0.1%)	0	2 (1.2%)	1 (0.3%)
Hyperglycaemia	0	0	2 (1.2%)	0
Dose Escalation Phase				
Subjects discontinuing treatment due to any AE	**58 (4.3%)**	**377 (17.0%)**	**10 (5.9%)**	**69 (20.7%)**
Nausea	1 (<0.1%)	112 (5.1%)	0	28 (8.4%)
Vomiting	1 (<0.1%)	14 (0.6%)	0	7 (2.1%)
Headache	6 (0.4%)	32 (1.4%)	0	4 (1.2%)
Depression	4 (0.3%)	3 (0.1%)	2 (1.2%)	2 (0.6%)

Data Source: Table ISS.S.6.3-3.1, Table ISS.S.6.3-1.1, NB-304 CSR Table 14.3-11A, and Table 14.3-11B.
Includes only AEs with 'drug stopped (primary)' as the reason for treatment discontinuation.
Dose Escalation Phase: Adverse events that occurred within 35 days of first dose date for study NB-303 and within 28 days for the other studies.
For the Diabetic Dataset, the preferred term diabetes mellitus denoted worsening of diabetes mellitus.

Even though potential hepatotoxicity with elevated liver enzyme values was similar among NB and placebo patients (1.2% vs 1.1%), 0.2% of NB-treated patients (8 of 38 patients) discontinued the study due to elevated liver enzymes compared to 0.1% of placebo patients (2 of 16).

More NB-treated patients discontinued the study due to skin reactions (1.6% in the NB group compared to 0.7% in the placebo group), though overall, the occurrence of skin reactions was similar in both treatment groups. Also serious adverse events (systemic reactions) were similar in the two groups (3 in the NB group and 2 in the placebo group).

Post marketing experience

During the review of the application the MAH provided supplementary information on two spontaneous serious adverse reactions reported postmarketing in the USA.

One case referred to a patient with apparent exacerbation of existing Bell's palsy and the other to a patient who experienced an event of vomiting, sweating, asthenia, and convulsions.

2.6.1. Discussion on clinical safety

The clinical safety of NB is derived from a total of 24 studies in the NB clinical programme. It comprises 15 Phase 1, five Phase 2, and four Phase 3 studies. Three integrated datasets have been defined: The primary dataset, the overall dataset and the non-diabetic/diabetic dataset - all including data from all randomised patients who were administered at least one tablet of study treatment and had at least one investigator contact/assessment at any time after the start of study treatment. The three datasets are considered to be appropriate and adequate to facilitate the evaluation of the safety and tolerability of NB.

In addition, interim data have been provided from the ongoing Study NB-CVOT. These data are not included in the datasets outlined above and thus not contributing to the figures derived from the integrated datasets, but are discussed separately when appropriate.

Of the 3239 subjects receiving NB, 1663 (51.3%) received ≥ 365 days (1 year) of NB treatment and 1580 (48.8%) had exposures of ≥ 56 weeks (reflecting at least 52 weeks of exposure at the maintenance dose). The vast majority received the NB32 dose. The size of the safety database, both overall and in terms of long-term exposure is considered satisfactory.

The drop-out rate was relatively high, almost 50% both in the NB groups (NB16 and NB32) and the placebo group. Although drop-out rates are high in obesity trials, they have been seen lower than observed in the NB programme. The majority of patients discontinuing the treatment with NB did so in the first 8 weeks (approximately 25-34%).

Most patients were White (about 75%), female (about 82%) and between the ages of 45 and 64 years (about 53%). In the study of patients with type 2 diabetes (NB-304), patients were generally older and the gender distribution more balanced than in the other Phase 3 studies. Demographic data were well balanced across treatment groups.

Only 62 elderly patients aged ≥65 years received NB in the Phase 3 programme. However, there is more substantial experience in elderly patients in the ongoing CVOT study. Interim results from this study reveal poorer tolerability of NB in elderly than in non-elderly patients. Therefore the Applicant has agreed that NB should be used with caution in subjects age ≥65–<75 years and is not recommended to subjects ≥75 years.

Adverse events were more frequent on NB (about 86%) than on placebo (about 75%). This difference was more pronounced during the dose-escalation phase.

Nausea was the most common adverse event on NB affecting about one third of NB patients compared to about 7% of placebo patients. For NB patients, it peaked within 4 weeks and resolved in most patients by 24 weeks, but also caused many discontinuations. Anti-nausea medication was allowed, but the actual use was very limited.

Constipation and headache were reported by 18% and 17% in NB patients, respectively, compared to 7.2% and 10.4% in placebo patients. Vomiting, dizziness, insomnia and dry mouth were other frequent adverse events, which were more commonly seen in NB patients than in patients on placebo.

About 12% of adverse events occurring >0.4% and at least twice the incidence of placebo in the NB group were categorized as severe compared to about 7% in the placebo group.

As expected, patients with T2DM experienced more adverse events. However, the difference in the incidence of some adverse events between NB and placebo appeared more pronounced. A higher incidence of shift to higher creatinine among diabetic patients treated with NB compared to placebo was observed. This may be attributed to the slightly higher baseline creatinine observed among T2DM patients. T2DM was also associated with a higher incidence of gastrointestinal disorders, however, this is not considered to raise any major safety concerns. Concomitant use of NB and metformin is not considered to pose any safety concerns. Several adverse events exhibited a clear dose-response relationship, e.g. nausea, vomiting and dizziness.

CNS related safety

Psychiatric side effects and suicide have been a great concern with weight control agents, in particular since the withdrawal of Acomplia from the market. Generally, the evaluation of psychiatric events was acceptable, among others using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Depression and suicide/self-injury did not appear to occur more frequently with NB than with placebo. Anxiety appeared to be more common in NB-treated patients than in patients receiving

placebo. Insomnia was clearly more common during titration in the NB group than in the placebo group. The interim analysis of the CVOT study, which included more patients with psychiatric co-morbidity, is discussed below.

Reassuringly, the use of sedatives/hypnotics was similar between the treatment groups both at initiation and end of study medication, and no difference in new users of sedatives/hypnotics was seen between treatment groups. Cognitive symptoms were not frequent, but occurred three times more frequently on NB than on placebo.

Epileptic seizures - a well-known side effect of bupropion, especially at high doses – occurred in two patients on NB and none on placebo. A further seizure was reported in a patient on NB in the CVOT. The incidence was less than 0.1% which is the frequency estimate often given for bupropion. History of - or current - seizures should be (and has been proposed as) a contraindication. As no toxicology study was conducted with the combination, any potentiation of the convulsive effects of bupropion or its metabolites by naltrexone has not been investigated in the non-clinical setting.

The effects on cognitive function and seizure will be monitored in the Post marketing setting.

Although it may seem reassuring that, except for insomnia and anxiety, psychiatric events such as depression and suicidality were not more common in NB patients than in patients receiving placebo, the proportion of subjects with a history of depression at baseline was low in all Phase 3 trials. The studies therefore may not be representative of the target population who are likely to have a higher proportion of depression. The Applicant was requested to discuss the validity of the measures used to assess depression in these studies. Further, the Applicant was asked to discuss whether other CNS disorders have been adequately represented in the selected study population and provide reassurance that NB can be safely administered to these patients. The Applicant provided an analysis and discussion using interim results from the ongoing Study NB-CVOT. In this study (as per the interim analysis), 24% of subjects were on an antidepressant medication. The incidence of SAEs in the psychiatric class was low and comparable between treatment groups. It is noteworthy that the incidence of psychiatric adverse events leading to study discontinuation was about three times higher in NB-treated patients than those on placebo, with anxiety and insomnia being the main causes. Therefore, whilst it is accepted that there would appear to be little evidence of an effect of NB32 on the risk of depression or suicidality, there does appear to be an increased risk of anxiety, insomnia and cognitive symptoms, an effect which appears to be particularly prevalent in diabetic patients and those with a greater CV risk. The Applicant argues that the increased risk of anxiety and insomnia is likely to be a direct effect of the sympathomimetic actions of bupropion and not an effect on mood as such. This is considered a speculative, although not implausible explanation.

Other

There was a small, but increased incidence of patients with a marked increase in serum creatinine in the NB group compared to placebo. This was also reflected in the mean change from baseline by visit. The increase did not appear to progress over time. According to the Applicant, the likely reason is that bupropion and its metabolites competitively inhibit the OCT2 in the basolateral membrane of the renal tubule responsible for creatinine secretion. This explanation is accepted by the CHMP.

Naltrexone has been associated with hepatotoxicity. In the NB programme, these events were not clearly more common on NB than on placebo. However, more NB-treated patients discontinued the study due to elevated transaminases compared to placebo. Gallbladder events are sometimes seen in patients experiencing weight loss, but these events also occurred at similar frequencies in the NB and the placebo group.

Skin reactions – observed with both individual medicines - also occurred at similar rates (NB vs. placebo), but there were more discontinuations due to these events on NB than on placebo. Male sexual dysfunction occurred more frequently on NB than on placebo, but at low rates.

Cardiovascular safety

Bupropion is known to have sympathomimetic effects, and consequently cardiovascular safety is a key focus area for NB. Generally, one would expect weight loss to be associated with favorable cardiovascular (CV) effects, either evaluated using surrogates such as blood pressure, blood lipids and glycaemic parameters, or ideally using more robust clinical endpoints such as major adverse cardiovascular events (MACE).

However, NB was associated with smaller decreases in systolic and diastolic blood pressure than placebo. Even if the mean difference in change from baseline was small, the poorer performance of NB on reducing the BP as compared with placebo was a consistent finding irrespective of analysis method: a. looking at blood pressure as a continuous variable; b. categorical analyses of blood pressure; or c. analyses of increased blood pressure reported as an adverse event. Therefore, the CHMP considered necessary to mention this concern in the SmPC in relation to the need for discontinuation of treatment .

There was also an indication of an increase in heart rate with NB compared to placebo, albeit the difference was small. Tachycardia was more commonly reported with NB than with placebo. Finally, in the Phase 3 programme, MACE (by two different definitions) occurred more frequently in the NB group than in the placebo group.

Consequently, the CV safety of NB was a major concern to the CHMP. The Applicant has responded by providing interim results from the ongoing CVOT study. The primary purpose of this study is to investigate the CV safety of NB in weight management. The primary analysis based on the ITT population shows that statistically significantly more subjects treated with placebo (59 subjects, 1.3%) compared to NB (35 subjects, 0.8%) experienced MACE; hazard ratio (HR) (95%CI): 0.59 (0.39-0.90). Further, the secondary analysis of the PP population (referred to as on-treatment data) showed no difference between the placebo and the NB treatment groups (27 (0.6%) and 23 (0.5%) MACE events in the placebo and NB group respectively; HR (95%CI): 0.79 (0.45-1.38)). Hence, in both populations, the confidence interval for the hazard ratio was less than 2, which was defined as the non-inferiority margin in this interim analysis. Overall, the results are considered reassuring with regard to the short- and intermediate-term CV safety of NB as the results from the present interim analysis do not indicate an increased risk of major CV disease related to NB treatment. The incidence of MACE/Four point expanded MACE was correlated with neither weight loss nor decrease in blood pressure or heart rate.

The Applicant has provided the additional sensitivity analysis requested by the CHMP for the interim data from study NB-CVOT. In the original analysis, all MACE events were included, irrespective of the length of time between treatment cessation and the occurrence of the event. Whilst this allowed for capture of a larger number of events, it introduced some uncertainty into the conclusions drawn from the analyses, since events which occur after longer periods off-treatment may be less clearly related to the treatment, but influenced instead by other factors.

The analysis presented by the Applicant included events censored at different time points after discontinuation of treatment. Even when only on-treatments events are considered, the point estimate of the hazard ratio is still below 1, and the upper bound of the 95% confidence interval falls below 1.4. This provides some reassurance that the signal of no increase in MACE events from this interim analysis of data from the NB-CVOT study is not dominated by off-treatment events which may have been related to factors other than exposure to the treatment.

Furthermore, the CHMP requested that the applicant provides further information on the ongoing CVOT (Light trial) after 50% of event as a post authorization commitment.

The applicant has planned a new CVOT study (CVOT2), which will not mandate cessation of treatment in non-responders at 16 weeks. This will provide information on the safety and efficacy of exposure over longer periods and will give information on the continued need for the stopping rule.

The final study report is planned by 31 March 2022.

The CVOT2 study will be a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects. This study will monitor the long term CV risk (classified as MACE events) and is included as a condition to the Marketing Authorization (annex II of the product information).

Therefore, the CHMP requested to review the CVOT2 study protocol by 31 March 2015 for agreement. This study will be monitored regularly by a Data Monitoring Committee and the key aspects of the DMC charter will be provided to the CHMP, when reviewing the protocol. If the DMC recommends that the study is stopped prematurely, the applicant should inform the CHMP immediately and the final report will need to be submitted within 6 months after study discontinuation.

Since it is plausible that the off-treatment risk is correlated with the length of time on treatment, and in order to reduce the noise around signal of increased risk in those only exposed to treatment for relatively short periods, the CHMP recommends altering the design of the second study investigating cardiovascular safety planned by the Applicant (CVOT-2) with regard to the censoring of events. Whilst the CHMP agrees with the censoring of events occurring beyond 12 months after treatment discontinuation in those patients who received treatment for more than 12 months, two options are proposed for the censoring of events in patients receiving treatment for less than 12 months. In this group, events could either be censored after 6 months off treatment, or after a period equivalent to the time on treatment (e.g. in a patient on treatment for only 4 months, events beyond 4 months off treatment would be censored). The CHMP recommends that one of these designs should be incorporated into the design of study CVOT-2.

In the NB clinical trials, there was no evidence of treatment-related QTc prolongation in NB-treated patients. Cardiac arrhythmias were uncommon in the trials, and no instances of life-threatening arrhythmias were reported. This is in line with the experience with naltrexone and bupropion as individual medicines.

There was a tendency to lower lymphocyte counts in NB-treated patients than in patients in the placebo group. The Applicant addressed any association between the incidence of infections in the NB treated group and the reduction in lymphocyte values. Further data provided by the Applicant showed that subjects with lower lymphocyte counts have more infections/infestations than subjects with normal lymphocyte counts, but there was no apparent difference in the incidence of infections/infestations between the Total NB and the placebo group (45.4% vs. 44.0%). Moreover, there appeared no characteristic pattern in the infections/infestations reported among subjects with shifts to lower lymphocyte values, which is reassuring.

Other haematology and chemistry variables than the ones mentioned above were generally unremarkable with regard to effects of NB.

Because of no or very limited exposure, the safety datasets did not allow a direct evaluation of the safety in elderly patients (age ≥65 years), paediatric patients (age <18 years) or patients with renal or hepatic impairment. Consequently, NB should not be used in patients with moderate renal failure or mild or moderate hepatic impairment. NB is contraindicated in patients with severe and end-stage

renal impairment and hepatic impairment. Treatment of the elderly and patients with renal or hepatic impairment is sufficiently addressed in the SmPC.

Furthermore, the Applicant has presented a plan for the post-approval investigation of the safety and efficacy of NB32 in patients with renal and hepatic impairment, including multiple-dose PK studies as requested by the CHMP.

Use of NB in pregnant women was of course prohibited in the NB clinical programme. Nevertheless, there were 20 pregnancies in the NB group. None of them were reported to result in congenital abnormalities, but there were 4 spontaneous abortions in NB-treated pregnant women versus none in pregnant women who received placebo. The issue was raised to the Applicant, but it is agreed that the rate of spontaneous abortions observed in the NB group (20%) is within the normal rate. The Applicant has provided narratives for the four women with spontaneous abortion. Three of the four women had confounding factors potentially predisposing for spontaneous abortion. Use of NB during pregnancy should not be recommended. This is sufficiently addressed in the SmPC.

For drug-drug interaction, please refer to the sections on pharmacokinetics and pharmacodynamics.

No events of overdose were observed in the NB clinical programme. In the SmPC, management of NB overdose is described adequately.

Adverse events associated with withdrawal from NB were examined in Study NB-301. It included a 2-week blinded discontinuation phase for those subjects still enrolled at the end of the active treatment phase. There was no indication of withdrawal effects. The investigations to evaluate acute withdrawal effects are considered acceptable.

The majority of discontinuations due to adverse events occurred in the dose-escalation phase, where about 17% of the NB-treated patients discontinued the study compared to about 4% placebo treated patients. Nausea was the main culprit in these early discontinuations. During the entire treatment phase, about one quarter of the NB treated patients discontinued the study due to an AE. Again, nausea was the most frequent reason to discontinue in the NB treated patients.

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

2.6.2. Conclusions on clinical safety

The major objection regarding the cardiovascular safety of NB has been resolved with the interim data provided in the application together with additional sensitivity analyses. In addition, the CHMP considered the need to continue monitoring of CV safety and agreed with the Applicant's plans to investigate longer-term cardiovascular safety in a second cardiovascular outcome study (NB-CVOT 2). Further, the Applicant has presented a plan for the post-approval investigation of the safety and efficacy of NB32 in patients with renal and hepatic impairment.

From the safety database all events considered adverse reactions reported in clinical trials and post-marketing (monocomponents) have been included in the Summary of Product Characteristics.

The CHMP considers that the measures necessary to address issues related to safety have been adequately addressed in the RMP and are reflected in the annex II condition of the opinion.

2.7. Pharmacovigilance system

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk management plan

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

The PRAC considered that the risk management plan version 06 could be acceptable if the applicant implements the changes to the RMP as described in the advice.

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

The PRAC considered that the risk management plan version 04 is acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice with the following changes:

- addition of the indication to the key elements to be included in the prescriber guide

- change the proposed categorisation of the CVOT 2 study from category 3 to category 1 (Annex II condition)

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

The CHMP endorsed the Risk Management Plan version 08 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Seizures • Interaction with MAOIs, opioid analgesics, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6 • Transient increases in blood pressure or heart rate • Hypersensitivity reactions including severe reactions like Stevens-Johnson Syndrome • Neuropsychiatric symptoms • Hepatotoxicity • Gastrointestinal disorders (nausea, vomiting)
Important potential risks	• Suicidality in patients with depression • Off-label use and abuse potential • Cholecystitis associated with rapid weight loss • Congenital malformations
Missing information	• Use during pregnancy • Use during breastfeeding/lactation • Effect on fertility • Use in paediatric patients • Data on long-term use /chronic use beyond 1 year • Use in patients with hepatic impairment • Use in patients with severe or moderate renal impairment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
NB-CVOT study 1 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects With Cardiovascular Risk Factors Receiving Naltrexone SR/Bupropion SR(3)	Determine the effects of NB relative to placebo on major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in overweight and obese subjects who are at a high risk of having these events because they have diabetes and/or other cardiovascular risk factors.	• Major cardiovascular events • SAEs • AEs leading to study drug discontinuation • Exposure in patients with co-morbidities (e.g. depression) and on concomitant medications of interests (e.g. anti-depressants)	Started	First interim report May 2014; Second interim report (50% of events) targeted by mid 2015; Final study report planned for 4th quarter 2017

NB-CVOT study 2 – A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 4 Study to Assess the Effect of Naltrexone Extended Release (ER) /Bupropion ER on the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects with Cardiovascular Disease (1)	Determine the effects of NB relative to placebo on major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in overweight and obese subjects who are at a higher risk of having events because they have a history of cardiovascular disease with or without diabetes	• Major cardiovascular events • SAEs • AEs leading to study drug discontinuation • Relevant non-CV AEs of interest (e.g. neuropsychiatric events, hepatotoxicity, transient hypertension) • Exposure in patients with co-morbidities (e.g. depression) and on concomitant medications of interests (e.g. anti-depressants)	Planned	Study protocol : 31 March 2015 Study Enrolment: 2H 2015 Final study report: 1Q 2022
Naltrexone/ Bupropion (NB) **Drug Utilisation Study** (DUS): Retrospective Chart Review & Nested NB Prescribing Physician Cross Sectional Survey (3)	To evaluate how NB is used in real world medical practice:		Planned	Interim report: 24 months after NB launch Final study report:42 months after NB launch
	• To characterize users of NB	Age, sex and other demographics Patient comorbidity Patient subgroups for which there is missing information according to the RMP Women pregnant, breastfeeding, or seeking pregnancy Paediatric patients Patients with hepatic impairment Patients with severe renal impairment Potential off-label use and abuse potential, including use outside the indication and use in contraindicated conditions including bulimia, anorexia nervosa, patients using MAOIs		
	• To evaluate the pattern of use of NB	Dose and duration of treatment, including identification of long-term and chronic use, and changes in prescribing after week 16 of treatment Use of concurrent/ concomitant		

		medications with special focus on medications potentially interacting with NB or contraindicated, P450 enzymes metabolized drugs, opioids analgesics, MAOIs, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolized by CYP2D6 Specialty of the prescribing physician		
	• To assess the incidence of important identified and potential safety risks based on the RMP	• Seizures • Transient increase of blood pressure and heart rate • Hypersensitivity reactions • Neuropsychiatric symptoms • Hepatoxicity • Gastrointestinal disorders • Suicide and suicidal behaviour • Cholecystitis • Congenital malformations		
	• To evaluate the effectiveness of the Physician Prescribing Checklist as a tool for risk minimization. Goal 1: Was Physician Prescribing Checklist was Goal 2: Evaluate knowledge and awareness of target population Goal 3: Evaluate prescribing behaviour Goal 4: Evaluate impact on safety concerns	To evaluate whether physicians prescribing NB have received, understood and complied with the Physician Prescribing Checklist as part of physician packet provided prior to drug supply		
Naltrexone/ Bupropion **Observational Database Study** (3)	• To assess the incidence of important identified and potential safety risks based on the RMP	• Seizures • Transient increase of blood pressure and heart rate • Hypersensitivity • Neuropsychiatric symptoms • Hepatoxicity • Gastrointestinal	Planned	Interim report: After 1500 patients with NB is reached Second Interim report: 3

	• To characterize users of NB • To evaluate the pattern of use of NB	• Suicidal behaviour • Cholecystitis • Congenital malformations • Use in subgroups for which there is missing information e.g. pregnancy, breastfeeding, paediatrics patients • Use in contra-indicated populations • Use of concurrent/ concomitant medications potentially interacting with NB • Specialty of the prescribing physician		years after NB launch Final study report: 3 months after the 5 year analysis has been completed in the last country/ database
Renal impairment Study: Effect of Renal Impairment on the Pharmacokinetics of Naltrexone PR/ Bupropion PR Tablet (3)	• <u>Primary</u> To assess the PK following single and multiple dosing with NB in subjects with mild, moderate or severe renal impairment compared with subjects with normal renal function. • <u>Secondary</u> To assess the safety and tolerability of NB in subjects with renal impairment.	Missing safety information on use in patients with severe or moderate renal impairment	Planned	Final Report Submission: August 2017
Hepatic impairment Study: Effect of Hepatic Impairment on the Pharmacokinetics of Naltrexone PR /Bupropion PR Tablet (3)	• <u>Primary</u> To assess the PK following single and multiple dosing with NB in subjects with mild, moderate or severe hepatic impairment compared with subjects with normal hepatic function • <u>Secondary</u> To assess the safety and tolerability of NB in subjects with hepatic impairment	Missing safety information on use in patients with hepatic impairment	Planned	Final Report Submission: August 2018
A Phase 1, Open-Label Study to Assess the Effects of Repeated Dosing with Naltrexone Extended Release (ER)/Bupropion ER Combination	• <u>Primary</u> To assess the effect of NB at steady state concentrations on the single-dose plasma pharmacokinetics (PK) of metformin in healthy adult subjects.	Missing information on drug drug interaction with metformin	Planned	Final Report Submission: January 2017

Trilayer Tablets on the Single-Dose Pharmacokinetics (PK) of **Metformin** in Healthy Adult Subjects (3)	• Secondary To assess the safety and tolerability of the treatments received throughout the duration of the study.			
Thorough QT Study (3)	To confirm there is no effect of NB on QT interval as legacy programs for the mono-components bupropion and naltrexone did not include structured TQT evaluation	Missing information of effect of NB on QT interval	Planned	Final Report Submission: March 2017

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Seizures	SmPC includes current seizure disorder or a history of seizures on the list of contraindications (Section 4.3). The SmPC also includes text regarding seizures in Section 4.4 "Special warnings and precautions for use". The package leaflet includes the following text in Section 2: Do not take NB if you have a condition that causes fits (seizures) or if you have a history of fits. It also includes further text regarding seizures in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Interaction with MAOIs, opioid analgesics, drugs that inhibit, induce or are substrates of CYP2B6, and drugs metabolised by CYP2D6	SmPC includes patients receiving concomitant MAOIs, patients currently dependent on chronic opioids or opiate agonists (e.g., methadone), or patients in acute opiate withdrawal, on the list of contraindications (Section 4.3). The SmPC also includes text regarding patients receiving opioid analgesics in Section 4.4 "Special warnings and precautions for use". Section 4.5 further details interactions. The package leaflet includes the following text in Section 2: Do not take NB: - if you have a bipolar disorder (extreme mood swings);	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- if you are currently dependent on chronic opiates or opiate agonists (for example methadone), or you are going through acute withdrawal (cold turkey)*;* - *if you are taking medicines for depression or Parkinson's disease called monoamine oxidase inhibitors (MAOIs) or have taken them in the last 14 days;* *You should talk to your doctor, especially if you have a history of mania (feeling elated or over-excited, which causes unusual* behaviour). It also includes further text regarding MAOI and opiate in Section 2.	
Transient increases in blood pressure or heart rate	The SmPC includes uncontrolled hypertension on the list of contraindications (Section 4.3). There is also further text regarding hypertension in Section 4.4 (Special warnings and precautions for use). The package leaflet for NB states: Section 2 Do not take NB: If you have an abnormally high blood pressure (hypertension) that is not controlled using a medicinal product There is also further text regarding hypertension in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Hypersensitivity including Stevens-Johnson syndrome	The SmPC includes Hypersensitivity to the active substance(s) or to any of the excipients on the list of contraindications (Section 4.3). There is also further text regarding allergic reactions in Section 4.4 (Special warnings and precautions for use). The package leaflet for NB states: Section 2 Do not take NB: • if you are allergic to naltrexone, to bupropion or to any of the other	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	ingredients of this medicine	
Neuropsychiatric symptoms	The SmPC includes patients with a history of bipolar disorder and patients with a current or previous diagnosis of bulimia or anorexia nervosa on the list of contraindications (Section 4.3). There is also further text regarding Neuropsychiatric Symptoms and Activation of Mania in Section 4.4 (Special warnings and precautions for use). The package leaflet for NB states: Section 2 Do not take NB: if you have a bipolar disorder (extreme mood swings); • if you have an eating disorder or had one in the past (for example, bulimia or anorexia nervosa); There is also further text regarding mental health problems and mania in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Hepatotoxicity	The SmPC provides the maximum recommended daily dose of NB (Section 4.2) and includes text regarding hepatotoxicity in Section 4.4 (Special warnings and precautions for use) and Section 5.3 (Preclinical safety data). The package leaflet for NB details liver injury in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Gastrointestinal disorders (nausea, vomiting)	The SmPC provides the maximum recommended daily dose of NB (Section 4.2) and includes text regarding GI disorders (nausea, vomiting) in Section 4.8 (Undesirable effects) and Section 4.5 (Interactions). The package leaflet for NB includes nausea and vomiting in Section 4.	None
Suicidality in patients with depression	The SmPC includes text regarding Suicide and suicidal behaviour in Section 4.4 (Special warnings and precautions for use). The Package leaflet includes text regarding suicide in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off-label use and abuse potential	The SmPC includes text regarding therapeutic indication in Section 4.1, correct use of NB in Section 4.2 (Posology and method of administration), contraindications (Section 4.3) and Special warnings and precautions for use (Section 4.4). The Package leaflet includes text regarding correct use of NB in Section 1, Section 2 and Section 3.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist
Cholecystitis associated with rapid weight loss	The SmPC includes frequency of cholecystitis in Section 4.8 (Undesirable effects). The Package leaflet includes frequency in Section 4.	None
Congenital malformations	The SmPC includes text regarding pregnancy in Section 4.6 (Fertility, pregnancy and lactation) and Section 5.3 (Preclinical safety data). The Package leaflet includes text regarding pregnancy in Section 2.	None
Use during pregnancy	The SmPC includes text regarding use in pregnancy in Section 4.6 (Fertility, pregnancy and lactation) and Section 5.3 (Preclinical safety data). The Package leaflet includes text regarding pregnancy in Section 2.	None
Use during breast-feeding/lactation	The SmPC includes text regarding use during breastfeeding/lactation in Section 4.6 (Fertility, pregnancy and lactation). The Package leaflet includes text regarding breast feeding/lactation in Section 2.	None
Effect on fertility	The SmPC includes text regarding fertility in Section 4.6 (Fertility, pregnancy and lactation) and Section 5.3 (Preclinical safety data).	None
Use in paediatric patients	The SmPC includes text regarding use in paediatric population in Section 4.2 (Posology and method of administration) and in Section 5.1 (Pharmacodynamic properties).	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The package leaflet includes text regarding Use in children and adolescents in Section 2.	Checklist
Data on long-term / chronic use beyond 1 year	SmPC states the need for continued treatment should be re-evaluated annually (Section 4.2).	None
Use in patients with hepatic impairment	SmPC includes Patients with severe hepatic impairment on the list of contraindications (Section 4.3). The SmPC also includes text stating NB is contraindicated in patients with severe hepatic impairment and not recommended in patients with mild or moderate hepatic impairment in Section 4.2 (Posology and method of administration) and in Section 5.2 (Pharmacokinetic Properties), and provides further details in Special warnings and precautions for use (Section 4.4). The package leaflet includes contraindication in those with severe liver disease in Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with severe or moderate renal impairment	SmPC includes Patients with endstage renal failure or severe renal impairment on the list of contraindications (Section 4.3). The SmPC also includes text stating NB is contraindicated in endstage renal failure and severe renal impairment and is not recommended in patients with moderate renal impairment in Section 4.2 (Posology and method of administration) and in Section 5.2 (Pharmacokinetic Properties), and provides further details in Special warnings and precautions for use (Section 4.4) as well as in Section 4.8 (Undesirable effects). Section 4.2 (Posology and method of administration) states that for individuals who are at elevated risk for renal impairment, in particular, individuals with diabetes or elderly individuals, estimated glomerular filtration rate (eGFR) should be assessed prior to initiating therapy with naltrexone / bupropion. The package leaflet includes contraindication in those with end-stage kidney disease in or severe kidney disease Section 2.	Physician educational kit, to reinforce indication and ensure appropriate patient selection, which contains: • SmPC • Physician Prescribing Checklist with a prompt for assessment of eGFR individuals at risk for renal impairment, particularly individuals with diabetes or elderly patients, prior to initiating NB therapy

2.9. Product information

In the product information, the expression of strength for each active substance is mentioned as a salt as it falls under one of the exception defined in the SmPC guideline as defined below :

'*In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed in situ.*'

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The clinical programme included four pivotal studies randomised, double-blind, multicentre, placebo-controlled conducted in obese and overweight subjects receiving customary diet and behavioural counselling, including prescribed exercise (Studies NB-301 and NB-303) and in obese/overweight subjects undergoing intensive lifestyle modification counselling (Study NB-302). One study was conducted in obese/overweight subjects with type 2 diabetes (Study NB-304).

Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI ≥30 and ≤45 kg/m^2 for subjects with uncomplicated obesity and with a BMI of ≥27 and ≤45 kg/m^2 for overweight or obese subjects with controlled hypertension and/or dyslipidaemia. The type 2 diabetes patients enrolled in Study NB-304 were to have a BMI ≥27 to ≤45 kg/m^2.

In NB-301, NB-302 and NB-304 studies, the mean weight loss change from baseline in the ITT analysis using LOCF as imputation method ranged from -8.1% to -3.7 % in NB group compared to -4.9% to -1.3% in placebo group at week 56. In NB-303 the mean weight loss change from baseline in the ITT analysis using LOCF as imputation method was -5.7% in the NB group compared to -1.9% in the placebo group at week 28.

Treatment with NB32 resulted in statistically significant weight loss compared with placebo in overweight/obese patients with or without hypertension or dyslipidaemia, as well as in overweight/obese patients with type 2 diabetes mellitus. The percentage of patients loosing ≥5 % weight loss ranged from 46% to 28% in the NB group compared with 34% to 12% in the placebo group (analysis in the Randomised population using BOCF as imputation method).

When using more conservative imputation methods, such as BOCF, the difference between NB and placebo diminished.

The weight loss with NB32 was modest-moderate. The placebo-subtracted weight loss with NB amounted to 3-4% when using the ITT analysis set and LOCF as imputation method – depending on study and study population. Using the criterion of ≥ 10% decrease in weight from baseline to endpoint, the NNT was 4.8 (Phase 3) and 11.1 (NB-CVOT).

The weight loss was accompanied by favourable effects on a number of secondary efficacy variables such as waist circumference, blood lipids (mainly HDL-cholesterol and triglycerides) and hs-CRP. There were also favourable effects in glycaemic control, both in non-diabetics but particularly in patients with type 2 diabetes.

The efficacy appeared stable over approximately one year and robust across various demographic and baseline characteristics.

In conclusion, the efficacy results suggest a modest effect of NB32 in producing weight loss.

Uncertainty in the knowledge about the beneficial effects

There is uncertainty regarding the true size of the effect given the high drop-out rate (around 50%), and the use of an imputation method for missing data (LOCF) which may overestimate the treatment effect. The conducted sensitivity analyses point to a lower treatment effect than the one calculated for the primary analysis.

Although some data have been provided to show an effect of treatment on secondary outcome variables, such as waist circumference, insulin resistance and glycaemic control in diabetic patients, firm conclusions of a reduction in the risk of progression to type 2 diabetes or improved glycaemic control in diabetics are difficult to draw from the data, and in any case, remain secondary to a primary effect on weight, which is modest.

There is also uncertainty about the efficacy in elderly patients (over 65 years of age) because only very few elderly patients were included in the Phase 3 trials, although the interim analysis of the

ongoing Study NB-CVOT did indicate efficacy in elderly patients to be similar to that seen in non-elderly patients.

A dedicated study in patients with type 2 diabetes suggested less efficacy in these patients when compared to non-diabetic subjects. However, data from the ongoing NB-CVOT study provide reassurance in this respect.

An analysis of efficacy by BMI strata based on the Phase 3 programme indicated that the weight loss was more pronounced in patients with the lowest BMI. However, this uncertainty about the relevance of the effect of NB in patients with the highest need of weight loss has been reduced significantly by interim data from the ongoing NB-CVOT study with considerably larger patient numbers. These data showed comparable efficacy across all investigated BMI groups.

Risks

Unfavourable effects

A number of adverse events were more common in patients receiving NB than in patients on placebo, most notably nausea, but also constipation, headache, vomiting, dizziness, insomnia and dry mouth appear to be frequent adverse reactions to NB.

Several adverse events appeared mostly during the titration phase. A considerable part of early discontinuations on NB can be attributed to adverse events.

The mean change from baseline at 1 year in systolic blood pressure in the pivotal studies was -1.6 mmHg in placebo subjects and -0.3 mmHg in NB subjects. The change in diastolic BP was similar. In the NB-CVOT study, the respective figures were +0.2 mmHg in placebo subjects and +0.7 mmHg in NB subjects. In the pivotal studies, the increase in systolic BP in NB subjects was most noticeable in those patients either not losing weight, or losing less than 5% of bodyweight. In NB-treated patients who lost at least 5% of body weight, the blood pressure decreased, though by a smaller amount than in placebo patients.

In the pivotal studies, the mean heart rate in the placebo group generally fluctuated from baseline by ±1 bpm, while mean heart rate in NB patients tended to increase by approximately 2 bpm above baseline.

Cognitive symptoms were not frequent, but occurred more frequently on NB than on placebo.

It is likely that NB in rare cases will cause epileptic seizures since bupropion is known to lower the seizure threshold. The same applies to other infrequent adverse reactions of naltrexone or bupropion (hepatotoxicity, skin reactions).

Except for insomnia and anxiety (mainly during titration), psychiatric events such as depression and suicidality were not more common in NB patients than in patients receiving placebo. This also applied to the ongoing cardiovascular outcome study which enrolled patients with a higher degree of psychiatric comorbidity than did the Phase 3 studies.

Even though the numbers are very small, in clinical studies, the number of MI events was higher in the NB group compared to the placebo group. However, based on interim results from the ongoing cardiovascular outcome study, NB appears not to be associated with an excess incidence of major adverse cardiovascular events (MACE). This provides reassurance about the cardiovascular safety in the short and intermediate-term.

Uncertainty in the knowledge about the unfavourable effects

There is uncertainty about the safety and tolerability in elderly patients, in patients with renal or hepatic impairment and in patients with various co-morbid conditions often associated with overweight/obesity because of no or limited experience in these subpopulations. In addition, interim

results from Study NB-CVOT suggest poorer tolerability in elderly patients and patients with renal impairment. Appropriate restrictions have been inserted in the SmPC for elderly patients and patients with renal or hepatic impairment. The use of NB in renal and hepatic impairment should be further investigated in the post-authorisation setting.

Although results on depressive and suicidal symptoms may appear reassuring, there is still some uncertainty about adverse CNS (including psychiatric) effects in at risk populations because the baseline incidence of psychiatric and other CNS illnesses in the study population was low. However, Study NB-CVOT included patients with more psychiatric co-morbidity than the Phase 3 studies, and interim results did not indicate excess depressive and suicidal symptoms in patients treated with NB compared to placebo.

There is also some uncertainty as to whether the incidence of seizures will be higher than with licensed bupropion medicines since the bupropion dose in NB is higher and because any potentiation of the convulsive effects of bupropion by naltrexone is unknown. Also, it is known that certain factors increase the predisposition to seizure with bupropion, such as concomitant use of antidepressants, alcohol abuse, and diabetes treated with hypoglycaemics or insulin. Such factors may be a feature in the target population for NB and could potentially increase the seizure risk.

However, although the daily dose of bupropion with NB will slightly exceed the daily dose when bupropion is used in its licensed indications, there are PK data to support that the exposure both in terms of peak concentrations and AUC following recommended doses of NB will be very similar to the exposure following recommended doses of bupropion in its licensed indications. Furthermore, the seizure rates in the NB clinical programme are low and have not exceeded the rates from the bupropion licensed indications. This also applies to the ongoing NB-CVOT study which allowed inclusion of patients with a wider range of comorbidities .

Although the interim results are reassuring with regard to cardiovascular safety in the short and intermediate-term, there is some uncertainty with respect to long-term cardiovascular safety given the effects of NB on blood pressure. The Applicant plans to evaluate the utility of continuing the ongoing NB-CVOT ("LIGHT" trial) after the second interim analysis early 2015.

Furthermore, monitoring of the long term cardiovascular safety will continue to be assessed through the planned CVOT-2 trial and provide more information regarding the CV risk in a higher risk population compared with the NB-CVOT trial.

The clinical implications of a low, but increased incidence of patients with a marked increase in serum creatinine in the NB group compared to placebo are unknown. However, the increases appear not to progress over time and are probably explained by bupropion and its metabolites competitively inhibiting the OCT2 in the basolateral membrane of the renal tubule.

Balance

Importance of favourable and unfavourable effects

The magnitude of weight loss in overweight/obese patients in the range of what NB has accomplished in the clinical trials is considered marginally significant but clinically relevant. It is not known with certainty whether this will translate into benefits in terms of physical and mental health, although there is some support for the notion that even a modest weight loss maintained over a long period results in health benefits.

The adverse events commonly associated with NB (primarily nausea, but also insomnia and anxiety) are bothersome for patients, but they are easily manageable: patients can stop taking the medication. The relatively high frequency of such events will therefore affect adherence to treatment.

However, other adverse events may be less easily manageable. The established potential of NB (because of the bupropion component) to cause seizures is important- even if it is a rare event, as is the propensity of NB to cause cognitive deficits.

The interim data available for the CVOT study provide further supportive data with regards to the CV safety profile in term of MACE events.

Benefit-risk balance

The efficacy of NB in weight management is limited, but when viewing the results of the primary endpoints as well as the secondary glycaemic and lipid-related endpoints in totality, it is considered to be clinically relevant.

This benefit combined with no evidence of a significant increase in cardiovascular adverse events in the short- to intermediate-term and the apparent lack of potential to cause depression and suicidal behaviour should be weighed against reasonably manageable tolerability issues (mainly gastrointestinal) and an important, but small increased risk of seizures.

In conclusion, this benefit compared with safety profile is adequately addressed in the indication highlighting the need to discontinue treatment after 16 weeks if patients have not lost at least 5% of their initial body weight.

Discussion on the benefit-risk assessment

The benefits are considered to outweigh the risks. The previous major reservations about cardiovascular safety and about other safety and tolerability concerns in the context of the limited efficacy have been resolved to an extent that does not preclude licensing. They are also adequately addressed in the post marketing setting. Two studies will investigate cardiovascular safety, the ongoing CVOT1 and the planned CVOT2 which will address long term cardiovascular safety, included as a condition to the Marketing authorisation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the risk-benefit balance of Mysimba is favourable as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight (see Section 5.1)

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 agreeed 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post Authorisation Safety Study : The MAH should conduct and submit results of a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone extended release (ER) /bupropion ER on the occurrence of major adverse cardiovascular events (MACE) in overweight and obese subjects. The study is to be monitored regularly by a Data Monitoring Committee (DMC). The study protocol, including key aspects of the DMC charter, has to be agreed before initiation of the study.	Submission of final study report by 31 March 2022 Submission of the protocol by 31 March 2015

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Mysimba is marketed, all healthcare professionals who are expected to prescribe Mysimba are provided with a prescriber guide. Prior to launch of Mysimba in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the prescriber guide with the National Competent Authority.

The prescriber guide shall contain the following key elements:

- a reminder of the indication and the need to discontinue treatment if there are concerns with the safety or tolerability of ongoing treatment, or if after 16 weeks patients have lost less than 5% of their initial body weight

- a reminder of the contraindications, warnings and precautions as well as patient characteristics that place patients at higher risk of adverse reactions to Mysimba, to help ensure appropriate patient selection.

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

Not applicable.

DIVERGENT POSITION DATED 18 DECEMBER 2014

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Mysimba indicated "*as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial Body Mass Index (BMI) of*

- ≥ 30 kg/m² (obese), or
- ≥ 27 kg/m² to < 30 kg/m² *(overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)*

Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

The overall benefit-risk balance for Mysimba in the claimed indication is considered negative due to:

1) A limited efficacy in weight management:

The weight loss on Mysimba 32 mg/360 mg was modest as mean weight changes from baseline was less than 10 % in all studies, and the difference from placebo did not exceed 5 % in any study (all-randomised set, Baseline Observation Carried Forward).

Although the main findings in the pivotal studies were that treatment with Mysimba 32 mg/360 mg resulted in statistically significant weight loss compared with placebo in overweight/obese subjects with or without hypertension or dyslipidaemia, as well as in overweight/obese patients with type 2 diabetes mellitus, the weight loss is considered too modest especially considering the safety concerns.

Furthermore, there are uncertainties regarding the maintenance weight loss and/or the rebound effect after treatment discontinuation.

Moreover, the efficacy of Mysimba has only been based on the body weight loss and not on its potential morbidity and mortality benefits during the clinical trial program.

2) Safety concerns:

- Uncertainties regarding neuropsychiatric risks: considering the composition of Mysimba (particularly with bupropion), the risk of depression and suicide is not appropriately described by available data to date of the adoption.

- Uncertainties regarding cardiovascular safety: available data (interim results of the ongoing Cardiovascular Outcome Trial study) to date of the adoption are insufficient and a strong long term data evaluation is mandatory to rule out this risk.

- Poor tolerability which might lead to poor adherence to treatment (about half of the patients discontinued prematurely): the relatively high frequency of such adverse events should affect adherence to treatment.

Overall, for these reasons, we consider that the benefit/risk ratio is negative for Mysimba in the management of obesity.

London, 18 December 2014

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David Lyons

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Joseph Emmerich