21 February 2013
EMA/CHMP/108692/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qsiva

International non-proprietary name: PHENTERMINE / TOPIRAMATE

Procedure No. EMEA/H/C/002350/0000

Note

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

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List of abbreviations

AE	Adverse event
AHI	Apnoea/hypopnoea index
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUC	Area under the drug concentration-time curve
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum observed plasma drug concentration
CPAP	Continuous Positive Airway Pressure
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DEXA	Dual energy X-ray absorptiometry
FDA	Food and Drug Administration
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment-insulin resistance
5-HT	Serotonin
IR	Immediate release
ISE	Integrated Summary of Effectiveness
ITT	Intent-to-Treat
IWQOL	Impact of Weight on Quality of Life
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	Least squares
MAA	Marketing Authorisation Application
MR	Modified release
OGTT	Oral glucose tolerance testing
PD	Pharmacodynamic
PK	Pharmacokinetic
PHEN	Phentermine

PPH	Primary pulmonary hypertension
QUICKI	Quantitative insulin sensitivity check index
SA	Scientific advice
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglycerides
TPM	Topiramate
TEAE	Treatment-emergent adverse event

1. Background information on the procedure

1.1. Submission of the dossier

The applicant VIVUS BV submitted on 17 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Qsiva, 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 24 June 2010. 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: "Qsiva is indicated for the treatment of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a mildly hypocaloric diet. Qsiva is recommended for obese adult patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI ≥ 27 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

The legal basis for this application refers to Article 8(3) of Directive 2001/83/EC - complete and independent application.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/223/2010 on the granting of a product-specific waiver.

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.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance phentermine contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 December 2008. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Qsiva has been given a Marketing Authorisation in the United States of America on 17 July 2012.

1.2. Manufacturers

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder **Co-Rapporteur:** Philippe Lechat

- The application was received by the EMA on 17 December 2010.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 April 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 April 2011.
- During the meeting on 19 May 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 20 May 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 November 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 December 2011.
- During the CHMP meeting on 19 January 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 24 May 2012.
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing/and or oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 17 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 14 September 2012.
- During the CHMP meeting on 20 September 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During a meeting of a SAG Diabetes and Endocrinology on 10 May 2012, experts were convened to address questions raised by the CHMP.
- During a meeting of a Cardiovascular Working Party on 6 June 2012, experts were convened to address questions raised by the CHMP, following which the CVS WP adopted a report on the CHMP List of Questions for Qsiva.
- During a meeting of a Pharmacovigilance Working Party on 18-20 June 2012, experts were convened to address questions raised by the CHMP, following which a PhVWP adopted a report addressed to CHMP.

- During a meeting of PRAC on 3-5 September 2012, experts were convened to address questions raised by the CHMP, following which PRAC adopted advice on CHMP request.
- During the meeting on 18 October 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Qsiva.

1.1. Steps taken for the re-examination procedure

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

Rapporteur: Ian Hudson Co-Rapporteur: Daniela Melchiorri

- The applicant submitted written notice to the EMA on 23 October 2012 to request a re-examination of Qsiva CHMP opinion of 18 October 2012.
- During its meeting on 15 November 2012, the CHMP appointed Ian Hudson as Rapporteur and Daniela Melchiorri as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 3 January 2013. The re-examination procedure started on 4 January 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 15 January 2013. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 23 January 2013.
- During a meeting of the Scientific Advisory Group Diabetes and Endocrinology on 1 February 2013, experts were convened to consider the grounds for re-examination
- During a meeting of the PRAC on 7 February 2013, advice was given to the CHMP on the proposed RMP
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 11 February 2013
- During the CHMP meeting on 18 February 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21 February 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

Problem statement

In the European Union, it is estimated that approximately 36% of adults are overweight (body mass index [BMI] ≥25 kg/m^2 and ≤29.9 kg/m^2) and 17% of adults are obese (BMI ≥30 kg/m^2). More males than females are considered overweight (>82 million and 61 million, respectively) while more females than males are considered obese (37 million and 31 million, respectively).

Obesity is associated with numerous co-morbidities, including dyslipidaemia, coronary artery disease, hypertension, stroke, obstructive sleep apnoea, and type 2 diabetes.

Epidemiological data indicate that obesity and being overweight are factors associated with an increased risk of death. Even a modest weight loss of 5% to 10% can result in a reduction in obesity-related metabolic and cardiovascular risk factors. Diet, exercise, and behaviour modification are standard treatments for obesity. However, many obese individuals do not achieve sustained weight reduction with this treatment option and in such situations pharmacological options may be of value as an adjunct to dietary measures and physical exercise. The only medication currently approved in the European Union for the treatment of obesity is orlistat. In severe obesity, very low calorie diets may be applied for a limited period of time. Additionally, surgery may be an alternative as a last resort.

Although no studies have as yet confirmed an effect on mortality or morbidity, weight reduction has been associated with reduction in blood pressure in both normotensive and hypertensive individuals, improvement in lipid profiles and improved glycaemic control in both patients without diabetes and patients with type 2 diabetes. Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight.

About the product

This application for Qsiva was submitted initially under the name Qnexa. The product had also the investigational name "VI-0521" and is authorised in the US under the name of Qsymia. It contains phentermine/topiramate which is frequently abbreviated throughout this report as PHEN/TPM.

Qsiva is a combination of phentermine and topiramate that contains lower doses of these components than are currently marketed world-wide as monotherapies for weight loss (phentermine) or other indications. The recommended dose of phentermine/topiramate contains phentermine 7.5 mg and topiramate 46 mg, which is approximately one-fourth the maximum approved daily dose of phentermine (37.5 mg; 30 mg free base) in the United States and one-tenth the maximum approved daily dose of topiramate (400 mg) in the United States and European Union. Full-dose phentermine/topiramate (phentermine 15 mg and topiramate 92 mg) contains half of the maximum daily dose of phentermine and approximately one-fourth of the maximum daily dose of topiramate.

Phentermine/topiramate is a fixed combination product for oral administration that contains the VIVUS proprietary bead formulations of immediate release (IR) phentermine (PHEN) and modified (prolonged) release (MR) topiramate (TPM) in a hard gelatin capsule. PHEN provides IR of phentermine. TPM is formulated for MR of topiramate in order to lower maximum observed plasma drug concentration (C_{max}) and delay the time to reach the maximum plasma concentration (t_{max}) by 7 hours compared to the commercially available topiramate, which has a tmax of 2 hours.

Phentermine hydrochloride, a synthetic sympathomimetic amine, is an anorectic agent. It is not available in most member states of the EU, but is approved and used in the United States at a recommended dose of 37.5 mg/day as a short-term adjunct to a weight loss regimen based on exercise, behaviour modification, and caloric restriction. The primary mechanism of action producing weight loss is believed to be pharmacologically induced caloric intake reduction. Phentermine stimulates central release of norepinephrine. It is postulated that increased circulating catecholamines may cause appetite suppression by increasing blood leptin levels.

Topiramate, a fructose monosaccharide derivative with sulphamate functionality, is a neurotherapeutic agent approved for treatment of seizure disorders at recommended doses of 200–400 mg/day and for migraine headache prophylaxis at recommended doses of 100–200 mg/day. Several published clinical studies have shown that topiramate monotherapy produces significant weight loss in obese individuals and clinically meaningful improvements in glycaemic control and blood pressure. Available pharmacological evidence suggests that topiramate-induced weight loss results from increased energy expenditure, decreased energy efficiency, and decreased caloric intake.

Background of the use of phentermine in the EU

Phentermine, as an anorectic agent, was authorized nationally in the Union for treating obesity.

Following a class review of anorexic agents initiated in 1995, which included medicinal products containing as an active substance amfepramone, phentermine, clobenzorex, fenproporex, mefenorex, norpseudoephedrine and phendimetrazine, concerns in relation to the use of these medicinal products were raised, specifically regarding:

- lack of therapeutic efficacy in the treatment of obesity when assessed on the basis of accumulated scientific knowledge acquired over the years and current medical recommendations and
- concerns related to the safety profile of phentermine containing medicinal products regarding the potential risk for cardiac valve disorders with phentermine monotherapy, the risk of primary pulmonary hypertension and other serious cardiovascular and CNS adverse reactions such as dependence

As a consequence, the use of phentermine as an authorised medicinal product in the Union has been significantly reduced and therefore minimal safety information from post-marketing experience in the Union is available.

2.2. Quality aspects

2.2.1. Introduction

The finished product Qsiva is presented as modified-release hard capsules 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg. The product is a fixed-dose oral capsule combination of immediate-release phentermine (INN) as hydrochloride and prolonged-release topiramate (INN). The composition of the product is detailed in section 6.1 of the SmPC as it has been proposed by the Applicant.

The product is kept in a child resistant screw-capped, foil-sealed, HDPE bottle containing thirty (30) capsules with a desiccant.

2.2.2. Active Substance

Phentermine hydrochloride

Phentermine hydrochloride is a white crystalline, hygroscopic powder. It is soluble in water, methyl alcohol and ethyl alcohol, slightly soluble in chloroform and insoluble in ether. There is no evidence of polymorphism associated with phentermine hydrochloride. The substance is not optically active. Its chemical formula is $C_{10}H_{15}N$ HCl and its molecular weight is 185.69 g/mol. The chemical structure of phentermine hydrochloride is shown in the figure below.

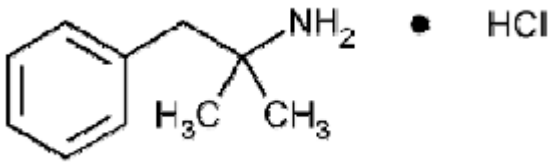


Figure 1: Chemical structure of phentermine hydrochloride

The information on the active substance phentermine is provided according to the active substance master file (ASMF) procedure within the current marketing authorisation application.

Manufacture

Phentermine hydrochloride is obtained from one manufacturer in accordance with the current Good Manufacturing Practices. A QP declaration issued by the Qualified Person has been provided.

Phentermine hydrochloride is manufactured in a two-step synthesis then crystallized, dried, sieved and packaged.

A comprehensive discussion on impurities and residual solvents was presented and the results were well within the limits set by the ICH guidelines Q3A and Q3C.

Confirmation of the structure of phentermine hydrochloride is provided by comparison of phentermine hydrochloride drug substance with USP Reference Standard (RS) by UV and IR techniques. In addition the structure of phentermine hydrochloride drug substance was confirmed by NMR spectroscopy, X-ray crystallography and differential scanning calorimetry.

Detailed information related to the manufacturing process including in-process controls, specification and control methods for intermediates, starting materials and reagents is detailed in the restricted part of the ASMF. This is considered acceptable.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, UV, Chloride reaction), loss on drying (gravimetry), residue on ignition (gravimetry), water (Karl-Fischer), pH, melting range, assay (HPLC and titrimetry), related substances (TLC and HPLC) and residual solvents (GC). The analytical methods used for testing the drug substance have been properly described and validated. The finished product manufacturer uses the same specification as the drug substance manufacturer.

Analytical methods have been adequately described and validated when necessary in accordance with ICH guidelines.

Batch analysis data has been provided for nine production scale batches from the active substance manufacturer. All results were within the specification limits.

The active substance is packaged in double, antistatic, non toxic low-density polyethylene bags. The filled bags are packed inside HDPE drums. A silica gel cartridge is placed between the two bags in order to preserve the drug substance from moisture. The packaging material complies with the Ph. Eur. and relevant legislation.

Stability

Stability studies have been carried out on 11 production-scale batches of phentermine in accordance with ICH conditions.

The parameters tested during stabilities studies were: assay, appearance, related substances and moisture. The analytical methods and limits were the same as those used for release testing of phentermine.

Long term studies for up to 5 years at 25°C /60% RH and accelerated studies for up to 6 months at 40°C/75% RH showed that no significant degradation could be observed and all the results remained

within the specification. Stress stability studies under heat, acid, basic, light and oxidative conditions were performed. Minimal degradation was observed under light and oxidative conditions.

Stability data under long-term and accelerated conditions, as well as forced degradation studies support the re-test period.

Topiramate

Topiramate is a white to off-white, non-hygroscopic powder. It is soluble in methanol and acetone and slightly soluble in water. The solubility of topiramate in water is pH-dependent. There is no evidence of polymorphism associated with topiramate.

Topiramate has four chiral centers and one L-Form isomer. There is no potential for geometric isomerism in the manufacturing process of topiramate. A specification for particle size has been established based on data from clinical batches. Its chemical formula is $C_{12}H_{21}NO_8S$ and its molecular weight is 339.36 g/mol,

The chemical structure of topiramate is shown in the figure below.

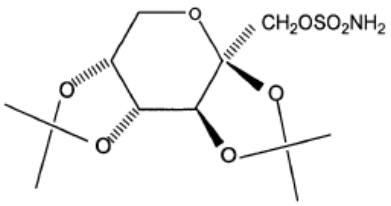


Figure 2: Chemical structure of topiramate

The information on the active substance topiramate is provided according to the active substance master file (ASMF) procedure within the current marketing authorisation application.

Manufacture

Topiramate is obtained from one manufacturer in accordance with the current Good Manufacturing Practices. A QP declaration issued by the Qualified Person has been provided.

Topiramate is manufactured in a four-step synthesis from commercially available starting materials. The two last steps of the manufacturing process involve re-crystallisation followed by milling.

A comprehensive discussion on impurities and residual solvents was presented and the results were well within the limits set by the ICH guidelines Q3A and Q3C.

The structure of Topiramate has been confirmed by comparison to the USP reference standard by IR, MS and NMR. Polymorphism studies using X-ray powder diffraction (XRPD) analysis have shown that topiramate exists in a single crystalline form and does not show polymorphism.

Detailed information related to the manufacturing process including in-process controls, specification and control methods for starting materials, intermediates and reagents is detailed in the restricted part of the ASMF. This is considered acceptable.

Specification

Topiramate specification includes tests for: appearance (visual), identification (FT-IR and HPLC), residue on ignition (gravimetry), water content (Karl Fischer), heavy metals, melting range, specific rotation (polarimetry), particle size distribution (particle size analyser), assay (HPLC), sulfamate and sulphate content (ion chromatography), related substances (HPLC and UV) and residual solvents (GC).

Analytical methods have been well described and validated when necessary in accordance with ICH guidelines.

The specification meets or exceeds the requirements of the USP Topiramate monograph. The specification limits for residual solvents are equal to or below the limits specified in ICH Q3C.

The finished product manufacturer uses the same specification as the drug substance manufacturer.

Batch analysis data on three batches tested by the drug substance manufacturer have been provided. The results are within the specification limits.

Topiramate is packaged in a double low-density polyethylene bags vacuum sealed in multi-layer laminate aluminium foil bag. The filled bags are packed inside HDPE carboy. The packaging material complies with the Ph. Eur. and relevant legislation.

Stability

Stability studies carried on three production batches kept in the commercial packaging and three production batches in the proposed packaging for marketing, under ICH conditions.

Parameters tested during stabilities studies are appearance, assay and related substances, water content by KF and sulfamate and sulphate content.

Long term studies (up to 12 months, 25 °C / 60% RH) and accelerated studies (up to 6 months, 40°C/75 %RH) showed that no significant degradation could be observed and all the results remained within the specification. Stress stability studies under heat, acid, basic, light and oxidative conditions were performed. Degradation was observed under acid and basic conditions. The analytical methods were found to be stability indicating.

Stability data under long-term and accelerated conditions, as well as forced degradation studies support the re-test period.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Qsiva is a hard gelatine capsule containing a multi-particulate formulation of the active ingredients phentermine hydrochloride (immediate release) and topiramate (prolonged-release) formulated as phentermine beads (PHEN Beads) and topiramate beads (TPM Beads).

The objective of the pharmaceutical development program for Qsiva capsules was to develop a once a day solid oral formulation of the two active substances. In addition, four dosage strengths were required, both to meet the needs of the clinical program, and for the proposed commercial product. This requirement led to the selection of multi-particulate phentermine beads (PHEN Beads) and topiramate beads (TPM Beads) that could be filled into hard gelatine capsules in appropriate amounts to achieve the different dosage strengths. To confirm that the desired release characteristics had been achieved both *in vitro* and *in vivo* studies were performed.

Since phentermine and topiramate do not come into direct contact with each other, compatibility studies were not deemed necessary however it was confirmed with compatibility studies that phentermine and topiramate were compatible with the excipients used for the beads. Also stability studies showed that phentermine was stable in the presence of the topiramate beads and vice-versa.

The formulation development and manufacture of the PHEN beads and the TPM beads was adequately presented. The choice of excipients in the TPM beads was based on the desired release profile and the experience at the manufacturing site.

With the exception of hard gelatine capsules, all the excipients used in Qsiva capsules are compendial excipients complying with the Ph. Eur. Hard gelatine capsule shells comply with satisfactory in-house specifications. The capsules components are compendial, the colouring agents comply with Directive 95/45/EC laying down specific criteria concerning colours for use in foodstuffs, printing inks are made with pharmaceutical grade raw materials. The quality of alcohol has been satisfactorily described.

The clinical formulation used for phase 1 and phase 3 clinical studies is identical to that used in the stability studies and for the commercial product, with the exception of the PHEN Beads loading levels that had no impact on the immediate release of phentermine.

According to the BCS classification, phentermine hydrochloride and topiramate are both high solubility and high permeability substances.

A level A in vitro/in vivo correlation (IVIVC) was established for the topiramate component of Qsiva capsules. The correlation was established with results from three batches. Internal predictability was found to be adequate. To perform internal validation, the model was used to predict the pharmacokinetic parameters C_{max} and AUC for Qsiva capsule batches that were used to construct the IVIVC model.

In-vitro dissolution results have been provided for all batches used in the clinical studies. The dissolution method complies with Ph. Eur. 2.9.3. The dissolution results obtained for phentermine at 30 minutes from all clinical and registration stability batches, at all dosage strengths were satisfactory. The dissolution results for topiramate from all clinical and registration stability batches were also very consistent regardless of strength.

The manufacturing process development from lab scale to production scale was extensively described for the PHEN beads, the TPM beads and the capsules and found to be satisfactory.

Qsiva capsules are packaged in high density polyethylene (HDPE) bottles with 1 gram of desiccant and a screw-on child resistant cap. The material in the HDPE bottle, the desiccant and the polypropylene cap comply with Directive 2002/72/EC. The desiccant is included in the bottle cap. The packaging used for bulk capsules has been described and also found to be acceptable.

Adventitious agents

The only excipient of animal origin in the Qsiva capsules is gelatine used for the capsules. Certificates of Suitability for the two different suppliers issued by the Ph. Eur. EDQM have been provided. No TSE risk was anticipated.

Manufacture of the product

The PHEN Beads and TPM Beads are manufactured by separate process and then filled in the capsule shells in order to achieve the four different strengths. A number of critical process parameters have been identified.

The beads are stored in bulk package until encapsulation.

The capsules are filled on a high-speed station capsule filler equipped with feeders for the two types of intermediate beads. For each capsule batch, the fill weights of the topiramate bead talc blend and of the phentermine beads are determined. 100 % of the capsules are weight sorted and visually inspected for defects.

Appropriate in-process controls and control of intermediates were performed during the manufacture of the beads and the capsules such as appearance, identification and assay for the PHEN and TPM beads.

No process validation on production scale batches had been performed at the time for submission. Until data from commercial scale batches has been provided, the accepted batch sizes correspond to the sizes of the pilot scale batches.

Product specification

The release and shelf-life specification for Qsiva include the following tests: appearance (visual), identification (HPLC -UV for phentermine and HPLC-RI for topiramate), phentermine assay (HPLC-UV), phentermine related substances (HPLC-UV), topiramate assay (HPLC-RI), topiramate related substances (HPLC-RI), sulfamate (ion chromatography), sulfate (ion chromatography), moisture content (Karl-Fischer, USP method), uniformity of dosage units (HPLC-UV for phentermine and HPLC-RI for topiramate, Ph. Eur. 2.9.40), dissolution (HPLC-UV for phentermine and HPLC-RI for topiramate, Ph.Eur.2.9.3), microbial contamination (Ph. Eur. 2.6.12 and 2.6.13).

The CHMP concluded that a second identity test based on different principle should be added for each drug substance.

Batch analysis data for three pilot batches of each strength were in accordance with the proposed specification. However, based on the available data, the CHMP concluded that the specification limits for topiramate assay at release in the drug product specification should be tightened In addition, the lower shelf-life limit for assay in the drug product specification should be tightened in accordance with the specification limit for total related substances,. Furthermore the upper shelf-life limit for topiramate assay should be tightened. The shelf-life limit for sulfate content should be tightened.

The analytical methods were adequately described and validated in accordance with ICH guidelines, and were shown to be stability-indicating.

Stability of the product

Stability data of three pilot batches of each dosage strength kept in the commercial packaging and stored for 12 months under long term conditions (25 °C / 60% RH), intermediate conditions (30°C / 65% RH) and accelerated conditions for up to 9 months (40°C / 75% RH) were provided. Stability conditions were in accordance with ICH requirements but only the highest and lowest strengths were tested based on a bracketing strategy. The batches were obtained according to the proposed manufacturing process.

Stability results under long term and intermediate conditions showed that the product remained stable and no significant degradation could be observed. However, the product was found unstable under accelerated storage conditions. The shelf life will be set based on the long term stability data.

A clinical batch was subjected to a freeze/thaw cycle. There was no significant change in any of the stability parameters indicating that Qsiva could stand accidental freezing.

Since the PHEN beads and the TPM beads can be manufactured at different time-points, stability studies were performed for the bulk PHEN beads and TPM beads. Based on the results, the CHMP concluded that further stability studies on PHEN beads and TPM beads stored in bulk were necessary, i.e., at least one batch of finished product should be prepared from the bulk of each intermediate, including bulk capsules, stored for the maximum claimed holding time. This finished product batch should be placed on stability under ICH conditions and tested until end of shelf-life.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture of the active substances phentermine and topiramate has been presented in a satisfactory manner. There are some outstanding issues regarding the quality of the finished product. No process validation for the proposed production scale batch size has been performed, therefore the largest batch size that can be accepted is that of the pilot scale batches. The specification of the finished product should be revised based on the batch data results and a second identity test method should be included for each drug substance. Further stability studies on PHEN beads and TPM beads stored in bulk are necessary.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the medicinal product is acceptable. There are no quality outstanding issues on the quality of the active substances at the time of the Opinion, however minor issues remain unresolved regarding the quality of the finished medicinal product: no process validation for the proposed production scale batch size has been performed, therefore the largest batch size that can be accepted is that of the pilot scale batches. The specification of the finished product should be revised based on the batch data results and a second identity test method should be included for each drug substance. Further stability studies on PHEN beads and TPM beads stored in bulk are necessary. These concerns were raised with the applicant during the procedure but were never adequately addressed.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP: Pivotal toxicity studies on the combination product sponsored by the applicant were conducted according to GLP as declared by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The acute anorectic effects of PHEN are well established from non-clinical studies and its clinical use. It is primarily mediated by the central actions of releasing catecholamine in the hypothalamus involving beta adrenergic and dopamine receptors but not 5-HT receptors. The neuropeptides cocaine-amphetamine-related transcript and neuropeptide Y and the gastro-intestinal peptide cholecystokinin may also be involved. The relative contribution of these mechanisms to the clinically observed activity of PHEN is not known.

TPM has multiple pharmacological mechanisms including modulation of voltage-gated ion channels, potentiation of GABA inhibition, inhibitory effects on kainite/AMPA type of excitatory glutamate receptors, and/or inhibition of carbonic anhydrase (CA) isozymes. One or more of the known pharmacological mechanisms of TPM may contribute to its long-term anti-obesity activity.

The additive activity of PHEN and TPM to decrease body weight was shown in a single study in a rat model of obesity. The body weight reduction in the combination group was significantly greater than in the single agent groups. Some referenced publication did not contain sufficient details of the study for full assessment; however, this was found to be acceptable, since the anti-obesity effect of Qsiva is subseqeuently assessed based on the clinical documentation.

Secondary pharmacodynamic studies

The pharmacodynamic profile of TPM was well-characterised in animals, whereas the information regarding secondary pharmacological effects from non-clinical studies of PHEN were parsimonious. Certain data on CNS effects are described in the section on Safety pharmacology.

However, the phentermine/topiramate clinical program has investigated the effects of phentermine/topiramate on endpoints that characterized its secondary pharmacodynamic profile, including glycaemic control, haemodynamics, lipid parameters, inflammation markers, mood and quality of life (see section on clinical studies below).

Safety pharmacology programme

The use of anorectics has been associated with increased incidence of PPH and valvulopathy. Mechanistically, pulmonary hypertension and drug-induced valvulopathy is associated with interactions with 5-HT transporters and increased synaptic circulating 5-HT levels. Neither phentermine nor topiramate has major effects on serotonin, indicating no expected serotonin-mediated effects. Administered alone, neither compound has been associated with pulmonary hypertension. There are no data from non-clinical in vitro or in vivo studies with PHEN on QT effects. However, the application did containt sufficient clinical data that address the risk for QT-prolongation. Thus, the knowledge of the pharmacological mechanisms of topiramate and phentermine in addition to the clinical experience with the combination of the two compounds superseded further non-clinical safety pharmacology studies whcih was accepted by the CHMP.

The structural, pharmacological and neurochemical profiles of PHEN are similar to that of amphetamine and PHEN has also an abuse potential which has been shown in several animal studies.

Pharmacodynamic drug interactions

2.3.3. Pharmacokinetics

The methods of analyses have been adequately validated. In rats, overall, PK of PHEN and TPM following co-administration was generally similar to that when dosed alone.

In rat, the exposure to TPM after repeated dosing was higher for females than for males. Further, the C_{max} and AUC increased in females after repeat dosing.

In the pregnant female rabbits (Toxicology Study 1060-043) dosed with a fixed-dose combination of PHEN and TPM, an approximately dose-proportional increase in TPM C_{max} and AUC_{0-24} was observed whereas PHEN increased more than dose-proportionally. PHEN and TPM C_{max} were generally similar between GD 6 and GD 18, while a decrease in AUC, -18% – 32%, was noted on GD 18 for TPM.

In dogs (Toxicology Study 1060-019) dosed with the fixed-dose combination, an approximately dose-proportional increase in TPM C_{max} and AUC_{0-24} was observed while PHEN increased more than dose-proportionally. TPM tmax occurred at 1 h post-dose and $t_{1/2}$ ranged from 1.8 to 2.9 h. There were no gender-related differences in PHEN or TPM PK in the dog. Following repeated dosing, TPM C_{max} and AUC_{0-24} values decreased (43%).

Co-administration of PHEN and TPM increased the systemic exposure to PHEN by approximately 30-50% in dogs. The increased systemic exposure to PHEN may be caused by increase in urine pH due to excess bicarbonate excretion related to TPM. However in rats and female rabbits, comparison of the groups receiving PHEN alone and in combination with TPM suggested no evidence for TPM affecting the exposure to PHEN. In clinical studies (OB-110 and OB-103), PHEN clearance was observed to be decreased in the presence of TPM.

Comparison of the groups receiving TPM alone and co-administered with PHEN suggested no consistent evidence for PHEN affecting the absorption and exposure of TPM. A similar comparison of the parameters obtained after administration of PHEN alone versus co-administration with TPM also indicated no substantial or consistent effect of TPM on the exposure to PHEN in rats. A significantly increased exposure was observed in rats and humans after prolonged administration but not in the dogs. The half-life of PHEN and TMP is notably longer in humans than in the animals. The relatively long half-life of PHEN and TMP in humans is most likely due to the low biotransformation compared to that in the rat.

PHEN and TPM exhibited low plasma protein binding. PHEN readily partitions into tissues including the brain and show no signs of accumulation in specific tissues.

TPM has low volume of distribution and distributes readily across blood-brain barrier, placenta and milk.

The metabolism of TPM in vivo is sufficiently described in animals and humans. A gender difference in both PHEN and TPM metabolism was observed in rats. Female rats have lower rates of metabolism compared to male rats, such that PHEN and TPM exposure in females tended to be higher than males. No relationship was observed between PK parameters and gender for either drug in clinical studies.

The Applicant has provided a discussion regarding the metabolic profile of phentermine in rat, rabbit, dog and human. According to available data N-oxidized metabolic products were formed to about <5% in the urine from human. There is no information about the metabolism of phentermine in the dog but in rat, also used in the repeated-dose toxicity studies, about 3% N-oxidation products were excreted in urine. This indicates that these metabolites also are formed in sufficient amount in plasma. Thus, N-oxidation metabolites were sufficiently covered in these studies. In rabbit, N-oxidized metabolic products accounted for 62% of the dose excreted in urine. There are no known unique human metabolites.

The major route of PHEN and TPM elimination was through urinary excretion. The rate of PHEN excretion was affected by urine pH. A more acidic pH causes a faster rate of PHEN excretion; a more basic pH causes a decrease in excretion, whereas changes in urinary flow rate had only a slight effect.

The ADME characteristics of PHEN and TMP in this combination product are well established and further non-clinical studies were not required in the view of the CHMP.

2.3.4. Toxicology

Repeat-dose studies with the combination of PHEN and TPM were conducted in rats up to 26 weeks and in dogs up to 13 weeks. These studies also contained one group each with the single components. In addition, the Applicant has undertaken a 2 years carcinogenicity study in rats with PHEN, which also provided long-term toxicity data. The Applicant has adhered to the advice received from the CHMP and member states.

Repeat dose toxicity

The selection of doses in repeat-dose studies were based on the results from 14 days studies in rats and dogs. However, no margin to clinical exposure was achieved in the 13-week dog study. In the 14-day dog study, a dose of 6/40 mg/kg/day caused weight loss of 39% in female dogs. The Applicant concluded that this dose would not have been well tolerated in the 13-week dog study and thus selected 4.5/30 mg/kg/day as the high dose to maintain the phentermine/topiramate dosing ratio consistent with the suggested clinical dose. This dose (4.5/30 mg/kg/day) is 75% of the dose used in the 14-day study (6/40 mg/kg/day), thus it is not expected that the higher dose would have given a much larger margin.

In the 13-week dog study 4.5/30 mg/kg/day caused weight loss in males, small weight gain in females, increased activity, stereotype, rapid breathing, panting and skin warm to touch. These effects were also noted in 4.5/0 mg/kg/day. At 0.45/3 and 0/30 mg/kg/day only minimal effects were observed. This suggests that the effects seen were mainly caused by phentermine and that there were no major additive/synergistic effects with the combination of phentermine and topiramate. Comparison with literature data of phentermine in a 26-week oral study in dog and a 3-month oral dog study with topiramate revealed no indication of additive/synergistic effects with the phentermine-topiramate combination.

In rats, except from expected body weight reduction which occurs already at the low doses the noteable findings are increased liver and kidney to body weight ratios (F) at 75 mg/kg TMP (4x (M), 7x (F) clin AUC) and minimal to mild centrilobular hepatocellular hypertrophy (M+F) as well as minimal to mild glandular/non-glandular hyperplasia in stomach (M+F) which also is associated with 11.25 mg/kg PHEN (3x (M), 5x (F) clin AUC). The changes were not observed in the recovery animals. The absolute liver weight decreased significantly in male rats dosed 11.25 mg PHEN which normalised after 4 weeks recovery. High dose TPM was associated with increased liver weights in females which were only partly normalised after the recovery period. The co-administration of PHEN and TPM chronically to rats did not seem to produce any additive or synergistic effects.

The findings in animals administered the PHEN/TPM combination were consistent with those noted in animals administered PHEN as a single agent.

The supportive information obtained from the literature (Ionamin SBA) is generally congruent with the results from the studies with the combination product i.e. decreased body weight and effects on liver.

Findings reported in the Topamax SBA for TPM were in line with the results obtained in the studies sponsored by the applicant, i.e. reduction in body weight and effects mainly on the liver but also the kidney, which however was not observed in the studies by the applicant.

Genotoxicity

PHEN and TPM are not considered to be either mutagenic or clastogenic.

Carcinogenicity

The applicant conducted a 2-years carcinogenicity study in rats with PHEN. Exposure at high dose was 11x (M), 15x (F) the clinical dose. No test article-related effects were seen in survival during this 2-year study.

As expected mean body weight was significantly lower in the treated animals than in the vehicle control in males and females in a dose-related manner throughout the study.

No effect of treatment was seen in haematology, macroscopic and microscopic pathology examinations. There were no test article-related differences in neoplastic or non-neoplastic microscopic findings between controls and treated males and females. Granular cell tumor incidence was slightly higher at the higher doses but with no statistical significance when comparing pair-fed and high-dose groups.

It can be concluded that the daily oral administration of PHEN for 2 years to Charles River CD rats did not produce any evidence of a carcinogenic effect.

In a mouse carcinogenicity study with TPM (Topamax SBA), tumors of smooth muscle origin in the urinary bladder were seen at oral dosages up to 300 mg/kg. This type of tumors has been reported to be unique to mice. Although the incidence was increased in treated mice, this bladder lesion was also seen in controls. The increased incidence in the treated mice may be secondary to the changes in urine pH produced by CA inhibition. There was no increase in tumors at any dose in either sex in a 2-year study in rats with TPM. Taken together, the findings do not indicate that Qsiva presents a significant carcinogenic risk to the patients.

Reproduction Toxicity

The applicant has not performed any fertility and early embryonic development toxicity studies for PHEN, TPM or the combination of the two.

In a three-generation reproductive toxicity study in rats with PHEN (Ionamin SBA), PHEN (40 mg/kg) substantially increased mortality and decreased body weight in the parental generation and, for the first and second cycles, produced decreases in the percent of pregnant females, mean live fetuses per litter, mean birth weight, and Postnatal Day 21 survival and pup body weights. In a second rat reproduction study, rats received PHEN orally at 2 and 5 mg/kg/day for a 5-day mating period. No effects were noted on fertility.

Fertility studies with TPM were conducted in male and female Sprague Dawley rats. The rats were dosed orally via gavage with 0, 0.2, 8, 25 and 100 mg/kg/day. In males, a small increase of testis weight was noted in all dose groups. When treated males were mated to untreated females, increased resorptions and post-implantation losses were noted. In treated females mated to untreated males, post-implantation loss was slightly increased at the top two doses at sacrifice on Gestation Day 13. In treated females, decreased corpora lutea and implantations, increased post-implantation loss and decreased pup weight at birth was noted.

The applicant has conducted embryo-foetal and pre/post-natal development studies on the PHEN/TPM combination in rats and rabbits; both studies included experimental groups administered either PHEN or TPM as single agents.

Results from the study in rats (1060-041) show effects on body weight and increased activity as expected. No evidence of teratogenicity and no effects on maternal macroscopic findings, uterine implantation data, or foetal sex ratios were observed in any group. Margin of exposure was 2-3x clin dose.

In the rabbit study (1060-043), no effects on maternal Gestation Day 18 blood pH levels, gross pathology, uterine implantation data, foetal sex ratios, and foetal body weights were observed in any treatment group, or on foetal external, visceral, or skeletal evaluations. In the group treated with TPM alone at 25 mg/kg/day, a slight increase in select skeletal aberrations (fused or absent ribs and/or fused, misaligned, malpositioned, absent, or misshapen vertebrae) was noted. These aberrations were noted to have occurred at a similar or higher incidence in the historical control data from the laboratory. However, the margin of exposure for TPM was only 1-2x clin dose in the HD groups.

There is no significant drug interaction between PHEN and TPM resulting in teratogenesis at doses tested.

Nevertheless, the teratogenic effects of TPM in multiple species, including humans, are well-established in the scientific literature and the lack of teratogenic effects in the present studies is most likely due to the low exposure to TPM. The choice of doses selected in the embryo-foetal toxicity studies in rats and rabbits were based on literature and dose-range finding studies. The margin of exposure in rats was 2-3 times the clinical dose and 1-2 times in rabbits, thus these studies have not gained sufficient margin to clinical exposure and can therefore not be adequately assessed. It is agreed that severe maternal toxicity limits the dose selection.

Rats (1060-042) were dosed on GD 6 and continuing throughout lactation up to and including LD 20. At the 11.25/75 mg/kg/day PHEN/TPM combination dose, test article-related effects in the parental generation animals included an increased activity, salivation, and excessive licking during lactation furthermore lower gestation and lactation weights, lower gestation weight gain, decreased food consumption during gestation and lactation, poor pup survival LD 0-4 (11 females failed to retain viable pups), and maternal neglect as evidenced by an increased frequency of lacerations/wounding and/or cannibalization of the F1 pups early in lactation (LD 0-4). Effects at this dose level in the F1 pups included lower pup body weights at birth and throughout lactation, delays in the onset of several physical developmental parameters (pinna detachment and eye opening), and delays in sexual maturation. The NOAEL for the PHEN/TPM combination treatment to the parental females, their litters, and F1 pups that continued on study was 1.5/10 mg/kg/day. These effects occurred at exposures similar to clinical.

Consequently, the suggested product information states that Qsiva is contraindicated in pregnancy, and in women of childbearing potential if an effective method of contraception is not used.

Other toxicity studies

The applicant has not conducted phototoxicity studies since TPM and PHEN do not absorb light in the UV/visible range (290 to 700 nm).

2.3.5. Ecotoxicity/environmental risk assessment

The results of the environmental risk assessment submitted with the application were found to be insufficient to conclude that Qsiva is unlikely to cause adverse environmental effects and that therefore no precautionary safety measures are needed to mitigate environmental risks, i.e. that no restriction regarding the disposal are necessary in the Product Information.

The CHMP recommended to conduct a complete ERA in line with the current EMA guideline (EMEA/CHMP/SWP/4447/00 corr 1) as amended by the Questions and Answers document (EMA/CHMP/SWP/44609/2010), also pointing out that the ERA should be performed separately for each compound within the medicinal product. The Applicant has initiated the conduct of a suite of studies, however these have not been completed during the procedure.

2.3.6. Discussion on non-clinical aspects

The use of anorectics has been associated with increased incidence of primary pulmonary hypertension (PPH) and valvulopathy. Mechanistically, pulmonary hypertension and drug-induced valvulopathy is associated with interactions with 5-HT transporters and increased synaptic circulating 5-HT levels. Neither phentermine nor topiramate has major effects on serotonin, indicating no expected serotonin-mediated effects. Neither compound alone has been associated with pulmonary hypertension. There

are no data from non-clinical in vitro or in vivo studies with PHEN on QT effects. However, there is sufficient clinical data that address the risk for QT-prolongation. Thus, the knowledge of the pharmacological mechanisms of topiramate and phentermine in addition to the clinical experience with the combination of the two compounds superseded, in the view of the CHMP, any need for further non-clinical safety pharmacology studies.

No margin to clinical exposure could be achieved in the 13-week repeat-dose toxicology dog study, and this was acceptable, since the Applicant's justification for dose selection, i.e. a significantly increased weight reduction at higher doses, was considered acceptable by the CHMP and together with the existing clinical experience this superseded the shortcomings of the study.

The Applicant has provided a discussion regarding the metabolic profile of phentermine in rat, rabbit, dog and human. According to available data N-oxidized metabolic products were formed to about <5% in the urine from humans. There is no information about the metabolism of phentermine in the dog but in rat, also used in the repeated-dose toxicity studies, about 3% N-oxidation products were excreted in urine. This indicates that these metabolites also are formed in sufficient amount in plasma. Thus, N-oxidation metabolites are sufficiently covered in these studies. In rabbits, N-oxidized metabolic products accounted for 62% of the dose excreted in urine. There are no known unique human metabolites.

In the embryo-foetal toxicity studies in rats and rabbits submitted for this application, the margin of exposure in rats was 2-3 times the clinical dose and 1-2 times in rabbits; thus these studies have not gained sufficient margin to clinical exposure and can therefore not be adequately assessed. It was agreed that severe maternal toxicity limits the dose selection. However, it should be noted that embryo-foetal lethality may mask possible teratogenic effects. Topiramate is a known human teratogen and this was proposed now to be clearly stated in the proposed SmPC and adequately addressed in the proposed RMP.

2.3.7. Conclusion on the non-clinical aspects

An additive effect of PHEN and TPM to decrease body weight was shown in a rat model of obesity. The anti-obesity effects of Qsiva studied in the clinical program superseded information from non-clinical studies, which was also the case with regard to the characterization of its secondary pharmacodynamic profile. The pharmacokinetics of the product were sufficiently described by the applicant. Repeat-dose toxicity studies with the combination of PHEN and TPM were conducted in rats up to 26 weeks and in dogs up to 13 weeks, and in addition the Applicant has undertaken a 2 year carcinogenicity study in rats with PHEN, which also provided long-term toxicity data. The program together with literature data was considered sufficient by CHMP. A teratogenic effect of TPM is well-established in the scientific literature in multiple species, including humans. A lack of teratogenic effects in the presented studies was considered to be due to low exposure to TPM. This was acceptable since severe maternal toxicity limited the dose selection. Nevertheless, as a consequence, the product information as suggested by the applicant during the procedure stated that Qsiva would be contraindicated in pregnancy, and in women of childbearing potential if an effective method of contraception would not be used.

Overall the information on the toxicological potential of Qsiva obtained from studies sponsored by the Applicant together with the supportive data obtained from the literature was considered to be sufficient as a basis for the assessment of the risks associated with this product. The Assessment of the Environmental Risk was considered incomplete, and the CHMP considered that no other non-clinical issues remained that would have precluded a potential authorisation of the product.

2.4. Clinical aspects

2.4.1. Introduction

The development programme/Compliance with CHMP Guidance/Scientific advice

This applicant took into account the development criteria presented in the following CHMP guidance documents:

- Clinical Evaluation of Medicinal Products Used in Weight Control (CPMP/EWP/281/96 Rev. 1) and
- Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1).

Scientific advice concerning preclinical and clinical development has been given by CHMP in December 2008. Some of the questions on the clinical development program were related to the study design (particularly to the comparator trial, the discontinuation of therapy, the synergistic effect and the dose rationale) and the safety profile of such combination.

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

QSIVA is a fixed combination of two drug substances: Topiramate and Phentermine hydrochloride. Topiramate is already approved and widely used in EU. However, phentermine is not available in most member states of the EU, but is approved and used in the United States.

Evidence for the efficacy and safety of phentermine/topiramate as a weight loss agent comes from a clinical development program that included four Phase 3 studies, five Phase 2 studies, and 11 Phase 1 studies. Table 1 summarises the number of randomised subjects in the phentermine/topiramate clinical development program. Table 2 summarises duration of extent of exposure throughout the phentermine/topiramate clinical development program.

Table 1: Number of Randomised Subjects in the phentermine/topiramate Clinical Development Program

		Number of Subjects by Treatment Group					
	Total Randomised	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92 or 15/100	PHEN/TPM Other Doses	PHEN/TPM (All Doses)	Placebo
Phase 1 Studies	686	125	107	225	195	527	98
Phase 2 Studies	355	--	--	177	--	177	178
Phase 3 Studies	4510	241	605	1615	--	2461	1617
ProgramTotal	**5551**	**366**	**712**	**2017**	**195**	**3165**	**1893**

Subjects enrolled in crossover studies may be counted under more than one treatment.
PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate.

Sources: OB-101 CSR, OB-102 CSR, OB-103 CSR, OB-105 CSR, OB-106 CSR, OB-107 CSR, OB-108 CSR, OB-109 CSR, OB-110 CSR, OB-118 CSR, OB-201 CSR, OB-202 CSR, OB-204 CSR, OB-205 CSR, DM-230 CSR, DM-231 CSR, OB-301 CSR, OB-302 CSR, OB-303 CSR, and OB-305 CSR

Table 2: Summary of the Extent of Exposure for the phentermine/topiramate Clinical Development Program

	Number of Subjects by Treatment Group					
	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92 or 15/100	PHEN/TPM Other Doses	PHEN/TPM (All Doses)	Placebo
Number of subjects dosed	366	712	2017	195	3165	1893
Number of subjects with ≥6 months of exposure	168	467	1328	--	1963	1206
Number of subjects with ≥12 months of exposure	143	349	1034	--	1526	869

PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate.

Sources: OB-101 CSR, OB-102 CSR, OB-103 CSR, OB-105 CSR, OB-106 CSR, OB-107 CSR, OB-108 CSR, OB-109 CSR, OB-110 CSR, OB-118 CSR, OB-201 CSR, OB-202 CSR, OB-204 CSR, OB-205 CSR, DM-230 CSR, DM-231 CSR, OB-301 CSR, OB-302 CSR, OB-303 CSR, and OB-305 CSR

2.4.2. Pharmacokinetics

The pharmacokinetics of phentermine and topiramate as a fixed combination product has been investigated in a total of 10 studies in healthy subjects and in 5 studies in patients. A total of 606 subjects were included and evaluated in the phase I studies with respect to pharmacokinetics.

Two population PK reports were provided including rich sampling from healthy volunteers and sparse samples from patients in phase II (OB-202 and DM-230) and phase III studies (OB-301, OB-302 and OB-303). The demographic factors weight, creatinine clearance, age, gender and race (Caucasians vs. Blacks) were explored for influence on pharmacokinetic parameters.

Pharmacokinetic parameters were in the majority of studies calculated by using non-compartmental methods. Standard statistical methods including ANOVA were applied.

The analytical methods employed have been properly validated including the in study performance of quality control samples.

Absorption

The median tmax observed in the studies are in accordance with the suggested SmPC wording, i.e. C_{max} is attained within approximately 6 hours for phentermine (range 2-10 h) and for topiramate 10 hours (range 7-16 h). The absolute bioavailability of phentermine has not been determined. The absolute bioavailability of topiramate has been reported to be 81-95 % for the European reference product.

Bioequivalence of the applicant´s formulation with the reference formulation has been established regarding extent of exposure. Bioequivalence between commercial formulation and the formulation used in pivotal phase III studies has been established for both active substances.

An in vitro study in Caco-2 cells was performed to evaluate the permeability of phentermine and topiramate. The applicant did not investigate if phentermine is an inhibitor of p-gp.

The applicant cited an article stating that topiramate is not a p-gp substrate, whereas another article, by Luna-Tortos et al from 2009, stated that topiramate is in fact a p-gp substrate. The responses provided by the applicant clarified that the results observed in vitro are divergent, however with a tendency towards topiramate not being a p-gp substrate. Hence, the CHMP agreed that the current

available information does not justify a warning against the concomitant use with p-gp inhibitors with respect to topiramate.

After intake of high-fat food, no significant food effect was observed (10 % decreased C_{max} of topiramate with high fat food). The product information therefore states that the product may be taken with or without food; this was agreed by the CHMP.

The applicant was asked to provide the observed trough concentrations in patients presented per dose level. The data supported the notion that the PK of topiramate and phentermine are independent of time and dose.

Distribution

The volume of distribution after intravenous administration of topiramate/phentermine has not been determined. After oral administration, the V/F of topiramate is 52-57 L. The protein binding is low for both substances, in the range of 18 % for phentermine and 13-17 % for topiramate. No investigation of any pH–dependent or concentration dependent binding was performed by the applicant. Based on literature and product information approved in Europe, it is stated that topiramate binds to a high-affinity low capacity saturable erythrocyte-binding site.

Elimination

The majority of the dose (both phentermine and topiramate) is excreted unchanged in urine, 70-80 % for phentermine and 70 % for topiramate. The applicant has provided a very brief summary of the metabolism and excretion of phentermine and topiramate.

Topiramate and phentermine are both metabolised to a limited extent. Based on in vitro data, the enzyme responsible for a limited metabolism of phentermine may be CYP3A4. Upon co-administration with anti-epileptics such as phenytoin and carbamazepine, the degree of metabolism of topiramate increases due to induction. Topiramate itself inhibits CYP2C19. Since carbamazepine is able to induce both CYP2C19 and CYP3A4, the induction could be due to induction of CYP2C19 or CYP3A4 (or both).

The applicant has provided an extended discussion regarding identified metabolites of phentermine and the percentage of dose identified and compared to the metabolism pattern in toxicological species. It can be concluded that there are a number of metabolites formed, the para-hydroxy metabolite and a number of N-oxide products (N-hydroxy, nitroso- and a nitrocompound) are excreted in urine. It is unlikely that there are human specific metabolites of major relevance when comparing with the preclinical data although data in plasma is lacking. In conclusion, while this information is somewhat limited and reliance on data from excretion with respect to safety should be made with caution, it was considered acceptable by CHMP since phentermine is already approved and used for 50 years and at a higher dose (30 mg).

The pharmacokinetics after intravenous administration is not known. Clearance (CL/F) and terminal half-life determined from oral administration of topiramate was approximately 22-36 ml/min (approximately 1.3-2.2 L/h) and 19-25 hours, respectively. The renal clearance of topiramate is in the range of 10-20 ml/min. Since fu x GFR is much higher than this value, re-absorption of topiramate must be larger than secretion.

Clearance (CL/F) and terminal half-life determined from oral administration of phentermine was approximately 8 L/hr and 21-24 hours, respectively. It has been observed that re-absorption is possible with phentermine, if the urine is alkalinised. No figure on renal clearance of phentermine has been provided.

Steady state of both phentermine and topiramate is expected after approximately 3-4 and 8 days of administration, respectively. The accumulation ratio of phentermine is somewhat higher than expected based on the estimated $t_{1/2}$ and once daily dosing (2.5- to 2.9-fold compared to the expected 2-fold accumulation for AUC and C_{max}). The accumulation of topiramate was somewhat higher than expected, being 3.7-fold at the high dose and 5.2-fold at the low dose (expected 2.9- to 3.1-fold). However, these differences may be caused by the rather large extrapolation observed between AUC_{inf} and AUC_t and therefore an uncertain determination of $t_{1/2}$.

Although the metabolism pattern has not been fully investigated, it was considered that each metabolite likely does not contribute to the activity to a significant extent as it has been assumed that the potency of each metabolite is low.

The applicant has not discussed the influence of genetic polymorphism. Given that the majority of the dose is excreted unchanged, this is acceptable.

Dose proportionality and time dependencies

The pharmacokinetics of phentermine and topiramate has been shown to be dose proportional and time independent with respect to exposure for doses between 3.75 mg /23 mg to 15 mg /92 mg of phentermine/topiramate respectively. With respect to C_{max} of topiramate, a tendency of a non-linear increase in C_{max} may be the result of a higher percentage of the higher doses being released more rapidly. This is also supported by the fact that Tmax occurs somewhat earlier for the higher strengths (12, 10 and 9 hours for the 3.75 mg /23 mg, 7.5 mg /46 mg and 11.25 mg/69 mg, respectively).

Special populations

The pharmacokinetics in target population at the recommended dose was evaluated. Preliminary, there are no signs of any large differences compared to healthy volunteers.

The applicant has investigated the exposure increase in patients with mild, moderate and severe renal impairment. Based on an up to two-fold increase in the exposure of both phentermine and topiramate in severe and moderate renal impairment, the dose is suggested not to go beyond 7.5/46 mg in subjects with moderate and severe renal impairment. In subjects with mild renal impairment the increase was less than 25%, and no dose adjustment is recommended. The titration in patients with severe renal impairment should follow a slower titration during the first 14 days, since dose dependent undesirable effects occur and in patients without renal/hepatic impairment, dosage increase to 15 mg/92 mg does not occur until 6 months after start of treatment, to reduce the initial tolerability issues (e.g. pulse rate increase). In patients with severe renal impairment (creatinine clearance 15-30ml/min), the exposure corresponds to a dose higher than 15 mg/92 mg at a dose of 7.5 mg/46 mg. Given that the normal dose in most subjects is 7.5 mg/46 mg and also given the increase in undesirable effects associated with the highest dose, the recommended maintenance dose in these patients should be 3.75 mg/23 mg, not higher. The applicant has changed the product information in accordance with this recommendation.

The Applicant was asked to provide a model (compartment pharmacokinetic model) including the relation between CL of Topiramate and Phentermine and creatinine clearance for the subjects in Study OB-106. Simulations of the proposed doses were made, however no simulation of the concentration-time profile with an alternative dose escalation was provided. Simulation of an every other day dosage during the first 14 days of titration show that an every other day posology of 3.75/23 mg in patients with severe renal impairment mimics the concentration time profile in the normal population adequately.

The applicant has stated that the effect of haemodialysis of phentermine has not been investigated. A cut-off value for creatinine clearance in end stage renal disesase (ESRD with creatinine clearance<15 ml/min or on dialysis) has been added to the product information as requested.

In patients with mild (Child-Pugh score 5-6)/moderate hepatic impairment (Child-Pugh score 7-9), there was an approximate 40 and 60 % increased exposure of phentermine as compared to healthy subjects. The applicant has explained that the observed exposure increase of phentermine in subjects with hepatic impairment, although the renal elimination is dominant, may be due to presence of renal tubular acidosis (RTA). In patients with RTA, the urine is not adequately acidified. Hence, the urine is alkaline, producing a higher percentage of phentermine uncharged and therefore increases the reabsorption leading to a higher exposure. The hepatic impairment patients with RTA does not have a reduction in creatinine clearance, therefore their renal function seems to be normal. Still, the patients with moderate hepatic impairment were not fully representative of decreased metabolic capacity and the difference in exposure as compared to healthy subjects is potentially even larger for phentermine, especially in subjects with severe hepatic impairment.

The recommended posology in patients with hepatic impairment is that dose escalation above 7.5/46 mg may only be considered in light of the degree of hepatic impairment and therapeutic benefit of the higher dose. The applicant has proposed during the procedure a dose escalation for the group of patients with mild hepatic impairment up to the highest dose. Patients with severe hepatic impairment have not been investigated. Given the results observed in moderate hepatic impairment and that these patients were not fully representative of decreased metabolic capacity, the exposure increase in severe hepatic impairment could be much larger. Therefore, a warning is now included in the proposed product information for the use in patients with severe hepatic impairment and the applicant has now also stated that the product should not be used in patients with severe hepatic impairment, given the unknown exposure increase.

Regarding titration in patients with moderate hepatic impairment, the oral clearance of phentermine in these patients is roughly 30% lower compared to patients with normal liver function. This translates into modest differences in the plasma concentration profile during the titration phase. For topiramate there was no difference in oral clearance between normal controls and different categories of hepatic impairment. Hence, a further adjustment of the titration regimen as proposed by the applicant was found not to be warranted by the CHMP.

Regarding the influence of gender, race, weight and elderly, preliminary there are no large effects observed. There is limited information of the PK in true elderly (>65 years). The age range in the studies was 18-71 years old. Over the studied age range there were no obvious trends. It had been proposed in the product information, section 4.2 and 5.2 of the SmPC, that the pharmacokinetics in subjects older than 70 years was not investigated. Given the overall lack of data in elderly, a warning was also proposed in section 4.4 of the SmPC.

The influence of race and gender preliminary does not warrant any dose adjustments. However, there is only limited information on the effect of race (Caucasians versus Blacks) on the pharmacokinetics of QSIVA since the majority of patients were Caucasian.

No investigation of the pharmacokinetics in children has been made. This is in accordance with the waiver granted from PDCO.

Pharmacokinetic interaction studies

In vitro studies phentermine

At 14-fold the unbound C_{max} of phentermine no inhibition of CYP2C19, CYP2B6 or CYP2C8 was observed. The concentration investigated is suboptimal but nevertheless, based on these data it is unlikely that an IC50/Ki is obtained at 50-fold unbound C_{max} or lower (where in vivo inhibition cannot be excluded) which was found to be sufficient by CHMP.

The applicant did initially not provide any details on the in vitro inhibition studies performed for phentermine on CYP1A2, 2C9, 2D6, 2E1, 3A4 or MAO-A and MAO-B, but provided details of the in vitro inhibition studies during the procedure and it can be concluded that there is no relevant inhibition by phentermine on systemic CYP1A2, 2C9, 2D6, 2E1, 3A4 or MAO-A and MAO-B. Intestinal inhibition of CYP3A4 cannot be excluded given the highest concentration tested and the anticipated intestinal concentration (1600-fold higher concentration in the intestine and the highest concentration tested). The SmPC, section 4.5, was suggested to have included information regarding the possibility for intestinal CYP3A4 inhibition.

Inhibition of CYP2B6 and 2C19 was claimed to have been observed for topiramate before and regarding CYP2C19, this information is included in the product information of the originator of topiramate in Europe. In addition, it is stated that topiramate induces CYP3A4. The submitted in vitro study on CYP2C8 inhibition is not conclusive. 16% inhibition was observed at concentrations 7-fold the unbound C_{max} of topiramate. It may not be completely excluded that there is in vivo inhibition of 2C8 at therapeutic concentrations. The product information was proposed to reflect this uncertainty.

The in vitro induction study performed showed that phentermine does not induce CYP1A2, 2B6 or 3A4 to a relevant extent compared to the vehicle. The largest margin used was 10-fold. A small decrease in the induction potential was observed with increasing concentrations (from 0.3 to 10 µM). No cytotoxic potential of phentermine was however observed.

In vivo

Study OB-107 evaluated the mutual interaction between phentermine/topiramate (15 mg/92 mg) and sitagliptin (100 mg q.d.), metformin (500 mg b.i.d.) administered to steady state and secondly to evaluate the effect of probenecid 2 g on phentermine/topiramate steady state pharmacokinetics. The pharmacokinetic parameters of phentermine and topiramate were not altered upon co-administration with metformin or sitagliptin, however the study design did not allow a new steady state to be reached for phentermine/topiramate. Probenecid was only administered during one day. It is now stated in the product information that the study was based on a single dose of probenecid. Metformin C_{max} and AUC were increased by 16 and 23 % respectively. Sitagliptin C_{max} and AUC were not altered upon co-administration.

Study OB-108 evaluated the influence of phentermine/topiramate doses to steady state on the pharmacokinetics of ethinyl estradiol and norethindrone. The C_{max} and extent of exposure of ethinyl estradiol was 8 and 16 % lower upon co-administration, respectively. The norethindrone C_{max} and AUC were increased by 22 and 16 %, respectively. Hence, there is no pharmacokinetic reason to state a caution, given that the gestagen is increased. However, given the known teratogenicity of topiramate, a contraindication for women not using an effective method of contraception is included in the product information. The applicant proposed to describe teratogenicity further in section 4.4.

Study OB-103 compared the relative BA of each individual component (phentermine and topiramate) of the fixed combination product versus the final formulation of phentermine/topiramate in obese adult subjects. Phentermine exposure was increased by 42 % when combined with topiramate, whereas the maximal concentrations, C_{max}, showed bioequivalence. The topiramate exposure and maximal concentrations of the fixed formulation were bioequivalent compared to when administered alone.

The interaction effect by topiramate on phentermine was comparable between study OB-110 and OB-103 (42 % versus 33 % increased exposure of phentermine), indicating that it is primarily a substance

effect, not a formulation effect. This interaction is likely due to the known inhibition of carbonic anhydrase by topiramate, resulting in alkalinised urine and increased re-absorption of phentermine. No formal investigation of the interaction between phentermine and topiramate has been performed at steady state. However, there is some evidence that the activity of Qsiva (weight loss) is linked to the additive effects of topiramate and phentermine rather than to solely the higher exposure to phentermine and therefore this was no longer considered a concern.

Given the high degree of renal excretion of both phentermine and topiramate, and the interaction observed between phentermine and topiramate, the applicant was asked to investigate the importance of renal transporters (reabsorption as well as active secretion transporters) in the elimination of phentermine and topiramate. The applicant has focused mainly on that phentermine is a substrate of carbonic anhydrase and that topiramate is unlikely to be a relevant inhibitor of OAT3 and OCT1. OCT1 is not a specific kidney transporter. The SmPC, as proposed by the applicant, would have included additional examples of carbonic anhydrase inhibitors and the applicant has prepared to perform further in vitro investigations regarding elimination of phentermine via other transporters on the secretion side, since active secretion of phentermine cannot be excluded. In the applicant´s proposed SmPC, the lack of information in this aspect is reflected. With respect to topiramate, there is no longer any request to evaluate topiramate as substrate of renal secretion transporters, given the dominance of re-absorption.

2.4.3. Pharmacodynamics

Mechanism of action

The primary mechanism of action of phentermine producing weight loss is believed to be pharmacologically induced caloric intake reduction. Phentermine stimulates central release of norepinephrine. Scientific literature postulate that increased circulating catecholamines may cause appetite suppression by increasing blood leptin levels. Increased norepinephrine levels may also result in a decrease in neuropeptide Y production, which may result in increased satiety and decreased appetite. The Applicant has not performed any specific PD studies to confirm the mechanism of action which is considered as acceptable considering the long term clinical experience.

Published clinical studies have shown that topiramate monotherapy produces weight loss in obese individuals and improvements in glycaemic control and blood pressure. Available pharmacological evidence suggests that topiramate-induced weight loss results from increased energy expenditure, decreased energy efficiency, and decreased caloric intake. No formal PD studies reflecting the mechanism of action have been performed, but this is considered as acceptable considering available scientific publications.

Primary and Secondary pharmacology

Drugs acting through catecholamine pathways, like phenteramine, have a stimulant or euphoriant effect which has been associated with potential for abuse. Cases of severe, often fatal, pulmonary artery hypertension (PPH) have been reported in patients undergoing therapy with certain centrally acting anorectic agents. This has been seen with the serotonin releasing agents, but not with the serotonin re-uptake inhibitors. Furthermore, phentermine and fenfluramine have been prescribed concomitantly until 1997 as an appetite-suppressant and have been associated with varying degrees of valvular regurgitation and PPH. Phentermine has not been associated with central or peripheral effects on serotonin.

In the QT-study, the heart rate-adjusted QTcSS showed no evidence of an effect of PHEN/TPM on QTc at the therapeutic level, and indicated only a marginal increase at the supra-therapeutic level. The

95% one-sided upper limit was always below 10 msec. Thus, the study did not indicate that PHEN/TPM has a propensity for QT prolongation. However, the PHEN/TPM group had a significant increase in heart rate at both the therapeutic and supra-therapeutic dose levels.

A study examining the psychomotor effect of PHEN/TPM was performed in healthy overweight subjects, The findings indicated that psychomotor functioning did not appear to be perturbed by PHEN/TPM. On the other hand, mild cognitive effects on aspects of attention (i.e., information processing speed and working memory) were found for PHEN/TPM 15/92 mg. In a PopPK/PD analysis including Phase 2 and Phase 3 data, phentermine and topiramate exposure (AUC) seemed to be important determinants of weight loss. The effect of phentermine and topiramate in PHEN/TPM on maximal percent weight loss appeared to be additive. Treatment with PHEN/TPM 15/92 mg resulted in a significant percent increase in heart rate compared to placebo.

2.4.4. Discussion on clinical pharmacology

Based on the provided data it is unclear if phentermine could act as intestinal CYP3A4 inhibitor and potential p-gp inhibitor, and if phentermine is substrate of active secretion transporter(s) in the kidney proximal tubule.

The dosing regimen in renal and hepatic impairment has been revised by the applicant following questions by the CHMP during the procedure. In patients with severe renal impairment a slower titration and lower recommended maintenance dose was considered necessary to avoid increasing tolerability issues and to decrease the risk of undesirable effects. For patients with hepatic impairment, the proposed dose adjustments were found to be acceptable by CHMP without further titration regimens. Use in end stage renal impairment and in severe hepatic impairment is not recommended. A cut-off value for ESRD has been provided in the product information (ESRD with creatinine clearance<15 ml/min or on dialysis).

2.4.5. Conclusions on clinical pharmacology

In conclusion, the mechanism of action is considered as sufficiently documented. The propensity to induce increased heart rate, the abuse potential and the possible effect on cognitive parameters is further described and discussed in the subsequent Section on Safety of this report.

2.5. Clinical efficacy

The PHEN/TPM clinical development program included four pivotal Phase 3 studies **(OB-301, OB-302, OB-303, and OB-305)** that evaluated the efficacy and safety of three fixed-dose combinations of PHEN/TPM for the treatment of obesity in individuals with and without weight related co-morbidities. In addition to the evaluation of weight loss, the program included evaluations of metabolic, cardiovascular, and glycaemic endpoints. The three doses studied were 15/92 mg (full dose), 7.5/46 mg (mid dose), and 3.75/23 mg (low dose).

The PHEN/TPM clinical development program also included five Phase 2 studies (OB-201, OB-202, DM-230, DM-231, and OB-204).

2.5.1. Dose response studies

No formal dose response studies have been performed. In the phase 2 studies, doses were chosen that reflected reductions compared to the approved labelled doses for both products included in the combination. The selected dosage of topiramate was one quarter of the FDA-approved dose for epilepsy or seizure (400 mg/day) and half of the approved dose for the indication of migraine

(200 mg/day), since tolerability problems with higher doses had been reported in literature. The selected phentermine maintenance dosage was half of the FDA approved daily dosage for adults (37.5 mg/day).

In the phase 3 studies this represented the highest ("full") dose (15/92 mg). The mid dose (7.5/46 mg) is proposed as the recommended dose. If weight loss goals have not been achieved after 6 months of treatment, titration to the 15/92 mg dose should be considered by using the intermittent dose 11.25 mg/69mg, but only in subjects responding and still have a BMI $\geq$ 35. Further, it is proposed that treatment should be initiated through dose titration starting with the 3.75/23 mg dose for 14 days followed by the daily dose of 7.5/46 mg.

The claimed dose of QSIVA 11.25 mg/69mg was not evaluated in any of the pivotal studies, but as it is only intended for up titration this was found to be acceptable by CHMP.

2.5.2. Main studies

Methods and Study Design

Studies OB-301, OB-302, OB-303, OB-305

OB-301 was a randomised, double-blind, placebo-controlled, multicentre, factorial study in obese adults, which compared full-dose and mid-dose PHEN/TPM with placebo and the respective single-agent PHEN and TPM components after 28 weeks of treatment. The study population included adult subjects ≤70 years of age with a BMI ≥30 kg/m^2 and ≤45 kg/m^2.

Subjects with type 2 diabetes were excluded from participation. Eligible subjects were assigned randomly to receive daily treatment with placebo, PHEN 7.5 mg, PHEN 15 mg, TPM 46 mg, TPM 92 mg, PHEN/TPM 7.5/46 mg, or PHEN/TPM 15/92 mg capsules.

Randomization was stratified by gender to ensure a similar distribution of male and female subjects across the treatment groups.

OB-302 was a randomised, double-blind, placebo-controlled, multicentre study in obese adults, which compared full-dose and low-dose PHEN/TPM with placebo after 56 weeks of treatment. The study population included adult subjects ≤70 years of age with a BMI ≥35 kg/m^2 (no upper limit). Subjects with type 2 diabetes were excluded from participation. Eligible subjects were assigned randomly in a 2:1:2 ratio to receive daily treatment with placebo, PHEN/TPM 3.75/23 mg, or PHEN/TPM 15/92 mg capsules. Randomization was stratified by gender to ensure a similar distribution of male and female subjects across the treatment groups.

OB-303 was a randomised, double-blind, placebo-controlled, multicentre study in overweight and obese adults with weight-related co-morbidities, which compared full-dose and mid-dose PHEN/TPM with placebo after 56 weeks of treatment. The study population included adult subjects ≤70 years of age with a BMI ≥27 kg/m^2 and ≤45 kg/m^2 with ≥**2** of the following weight-related co-morbid conditions:

- Elevated blood pressure, defined as systolic blood pressure (SBP) ≥140 mmHg and ≤160 mmHg (≥130 mmHg and ≤160 mmHg, if diabetic), diastolic blood pressure (DBP) ≥90 mmHg and ≤100 mmHg (≥85 mmHg and ≤100 mmHg, if diabetic), or requirement for ≥2 antihypertensive medications
- Elevated triglycerides (TG), defined as TG ≥200 mg/dL and ≤400 mg/dL or requirement for ≥2 lipid-lowering medications

- Fasting blood glucose level >100 mg/dL, glucose level >140 mg/dL at 2 hours post glucose challenge during oral glucose tolerance testing (OGTT), or diagnosis of type 2 diabetes managed with lifestyle measures or metformin monotherapy, and/or
- Waist circumference ≥102 cm for men or ≥88 cm for women.

Subjects with stroke, myocardial infarction, life-threatening arrhythmia, or coronary revascularization within the past 6 months as well as subjects with unstable angina, congestive heart failure (New York Heart Association Class II, III, or IV), or known or suspected clinically significant cardiac valvulopathy were not included.

Eligible subjects were assigned randomly in a 2:1:2 ratio to receive daily treatment with placebo, PHEN/TPM 7.5/46 mg, or PHEN/TPM 15/92 mg capsules. Randomization was stratified by gender and diabetic status.

OB-305 was a double-blind, placebo-controlled, one-year extension to study OB-303 to collect additional long-term safety and efficacy data on PHEN/TPM for a second year of exposure. The study population included subjects from selected sites who completed study OB-303 on treatment. Subjects who elected to enrol in this extension study continued on the same double-blind treatment they were on when they completed study OB-303 for up to 52 weeks of additional exposure. The analysis of weight change from week 56 to week 108 only included subjects who lost weight in study OB-303. Therefore the treatment comparisons are not randomised comparisons and should be interpreted with care.

Subjects in the Phase 3 studies followed a titration regimen during the first 4 weeks of double-blind treatment. Subjects assigned randomly to active treatment started titration with PHEN/TPM 3.75/23 mg taken once daily for 1 week before escalating to the next dose level. Dose escalation continued on a weekly basis until the subjects reached the dose level to which they had been assigned.

Subjects in the Phase 3 studies undergoing dose interruptions for any duration may have had the dose titrated back up to the original dose level based on the discretion of the investigator. Subjects whose treatment had been interrupted or discontinued were encouraged to remain in the study and to attend their regularly scheduled study visits.

In the pivotal studies, subjects with mild depression on stable therapy could be included. It is noted that elderly subjects > 70 years were not included and that the studies were performed exclusively in the US.

According to the Guideline on clinical evaluation of medicinal products used in weight control, subjects enrolled in obesity trials should be subject to an appropriate weight reducing diet run-in period for a specified minimum time. This was not the case in the pivotal studies. The importance of this deviation from the guideline is however considered as very limited.

The primary efficacy variables were percent weight loss with last observation carried forward (LOCF) and percentage of subjects with at least 5% weight loss at Week 28 with LOCF at end of study. These endpoints are considered as acceptable.

Participant flow

In studies 302 and 303 (1-year cohort), 66.1% of the randomised subjects (n=2482) completed all study visits. The most common reasons for discontinuation from the study were loss to follow-up (11.7%), withdrawal of consent (11.7%), and adverse event (5.1%). Of randomised subjects, 59.2% completed all study visits on study drug and 1527 (40.7%) subjects discontinued study drug.

A higher percentage of subjects in the PHEN/TPM groups than in the placebo group discontinued study drug due to an adverse event. A higher percentage of subjects in the placebo group than in the PHEN/TPM groups discontinued study drug for reasons of loss to follow-up, withdrawal of consent, and lack of efficacy. In study 301, 65.5 % of the study subjects completed visits on study drug, with similar proportions in all study groups. Study 305 enrolled approx. 27 % of the subjects that were initially randomised to study 303.

The proportion of subjects discontinuing the studies may seem large, but is comparable with other studies with weight lowering drugs. Discontinuation due to adverse events was most common in the groups receiving the combination PHEN/TPM 15/92 mg. In study OB-301 discontinuation of study drug due to adverse events was 7.3% with placebo, and 15.0% and 21.3% for the mid dose and for the high dose, respectively, with similar patterns in the other studies. Responder analyses for 5 and 10% responders have been calculated counting all withdrawals as non-responders. These analyses showed a clinically and statistically significant difference compared to placebo for 5, 10 and 15 % responders even though the proportion of responders were somewhat lower compared to the original analyses especially for 5% responders.

Baseline data

In studies 302 and 303 (1-year cohort), the majority of subjects were female (74.3%) and Caucasian (84.3%). The mean age of subjects was 48.3 years. At baseline, mean weight was 107.4 kg, mean BMI was 38.4 kg/m^2, and mean waist circumference was 115.7 cm. The PHEN/TPM 3.75/23 mg group(in study OB-302) had a higher mean weight, BMI, and waist circumference at baseline than the other treatment groups due to the inclusion criterion (i.e., baseline BMI $\geq$35 kg/m^2) in study OB-302. Overall, mean BMI at baseline in study OB-302 was 42.1 kg/m^2. The placebo group, PHEN/TPM 7.5/46 mg group, and PHEN/TPM 15/92 mg group were comparable with respect to demographic and baseline characteristics. Baseline characteristics in study 301 were similar to the 1-year cohort.

In study 303 (including subjects with co-morbidities), the most common conditions were hypertension, dyslipidaemia and impaired glucose tolerance. Approx. 16% of the subjects had diabetes. For other co-morbidities, 17% of the subjects had a history of depression while only 1.1 % of the subjects had a history of coronary artery disease. Thus, the experience in subjects with cardiac disorders seems to be very limited. Even though the effect in such subjects is not expected to be different compared to other patient groups, this is of importance for the safety evaluation.

Baseline characteristics in subjects included in the extension study OB-305 were similar to the overall population included in study OB-303.

Outcomes and estimation

Primary Outcome parameteres

Weight related outcomes

Mean percent weight loss from baseline, as well as the proportion of subjects reaching≥5% weight loss and ≥10% weight loss, both were of clear clinical relevance for the mid and the full dose in all main studies. In study OB-301 treatment with PHEN/TPM 15/92 mg resulted in a significantly greater percent weight loss after 28 weeks (9.0%) than PHEN 15 mg (5.8%), TPM 92 mg (6.1%), and placebo (1.5%), and PHEN/TPM 7.5/46 mg resulted in a significantly greater percent weight loss (8.2%) than PHEN 7.5 mg (5.2%), TPM 46 mg (4.9%). Similarly, data collected throughout the Qsiva clinical program, demonstrated that the response with the combination exceeds the response with either single agent.

The magnitude of weight loss achieved at month 3 predicted the results after 1 year of treatment. In the third 3-month response quintile (6.4% weight loss at 12 weeks), approximately 80% of subjects went on to achieve at least 5% weight loss at 1 year, with approximately 40% achieving at least 10% weight loss. Thus, a cut off of 5% seems relevant and has been used for other products.

Table 3. Percent Weight Loss at Study Endpoint – Individual Studies OB-301, OB-302, OB-303, and OB-305 – ITT Analysis

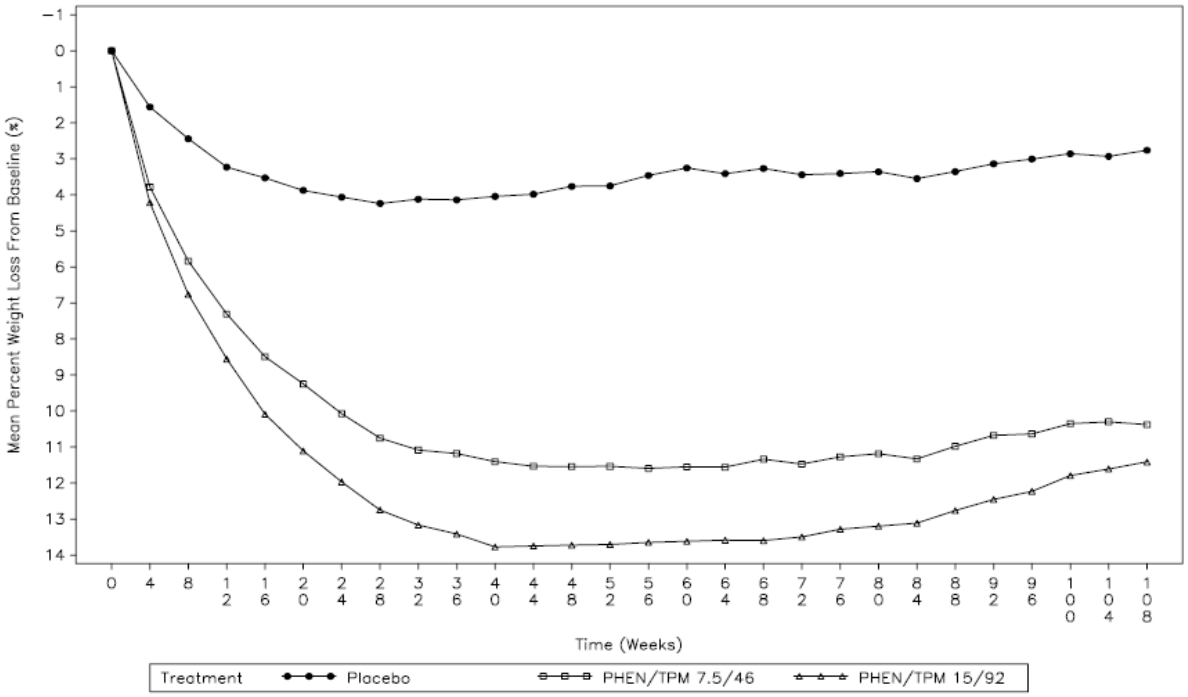
	OB-301			OB-302			OB-303			OB-305		
	Percent Weight Loss at Week 28 [1]			Percent Weight Loss at Week 56 [1]			Percent Weight Loss at Week 56 [2]			Percent Weight Loss at Week 108		
Treatment	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value
ITT LOCF												
Placebo	103	1.7 (0.61)	–	498	1.6 (0.40)	–	979	1.2 (0.28)	–	227	1.8 (0.55)	–
PHEN/TPM 3.75/23				234	5.1 (0.54)	<0.0001						
PHEN/TPM 7.5/46	103	8.5 (0.62)	<0.0001				488	7.8 (0.37)	<0.0001	153	9.3 (0.67)	<0.0001
PHEN/TPM 15/92	103	9.2 (0.61)	<0.0001	498	10.9 (0.39)	<0.0001	981	9.8 (0.28)	<0.0001	295	10.5 (0.50)	<0.0001

Table 4. Number (%) of Subjects With ≥5% Weight Loss and ≥10% Weight Loss at Study Endpoint – Individual Studies OB-301, OB-302, OB-303, and OB-305 – ITT

	OB-301			OB-302			OB-303			OB-305		
	Number (%) Reaching Threshold at Week 28 [1]			Number (%) Reaching Threshold at Week 56 [1]			Number (%) Reaching Threshold at Week 56 [2]			Number (%) Reaching Threshold at Week 108 [2]		
Treatment	N	n (%)	p-value	N	n (%)	p-value	N	n (%)	p-value	N	n (%)	p-value
≥5% Weight Loss												
ITT LOCF												
Placebo	103	16 (15.5)	–	498	86 (17.3)	–	979	204 (20.8)	–	227	68 (30.0)	–
PHEN/TPM 3.75/23				234	105 (44.9)	<0.0001						
PHEN/TPM 7.5/46	103	64 (62.1)	<0.0001				488	303 (62.1)	<0.0001	153	115 (75.2)	<0.0001
PHEN/TPM 15/92	103	68 (66.0)	<0.0001	498	332 (66.7)	<0.0001	981	687 (70.0)	<0.0001	295	234 (79.3)	<0.0001
≥10% Weight Loss												
ITT LOCF												
Placebo	103	7 (6.8)	–	498	37 (7.4)	–	979	72 (7.4)	–	227	26 (11.5)	–
PHEN/TPM 3.75/23				234	44 (18.8)	<0.0001						
PHEN/TPM 7.5/46	103	40 (38.8)	<0.0001				488	182 (37.3)	<0.0001	153	77 (50.3)	<0.0001
PHEN/TPM 15/92	103	42 (40.8)	<0.0001	498	235 (47.2)	<0.0001	981	467 (47.6)	<0.0001	295	159 (53.9)	<0.0001

In the 1-year cohort, the maximal weight loss was gained after approx. 36-40 weeks of treatment. No additional weight loss was seen in study OB-305 in the second year. Rather, there was a mean weight gain in all groups, most pronounced in the highest dose group, even though the results must be interpreted with caution due to the selection of subjects entering into study OB-305.

Figure 3: Percent Weight Loss Over Time – OB-303 and OB-305 – ITT – Intent-to-Treat Set



Baseline (Week 0) is defined as the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.

The additional weight loss with the high dose as compared to the mid dose was not impressive in study OB-301 while it was more evident in study OB-303. The additive effect seems to be most pronounced in subjects with higher baseline BMI.

Figure 4: Placebo-Subtracted Percent Weight Loss by Baseline BMI Category for the low, mid- and high dose of PHEN/TPM (Qnexa): 1-Year Cohort (ITT-LOCF)

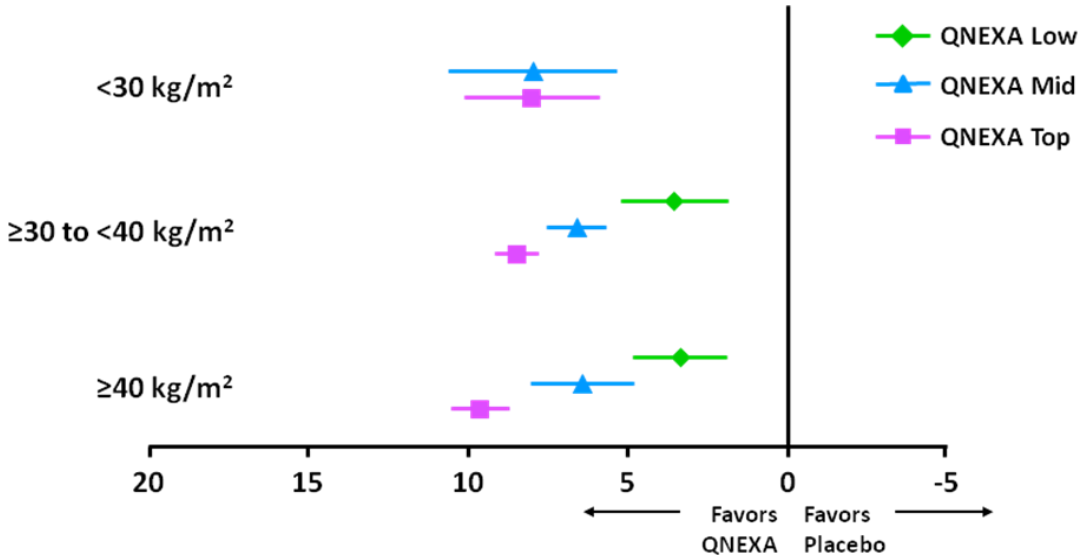


Table 4. Percentage of subjects with baseline BMI of ≥35 kg/m² who lost at least 5%, 10%, and 15% of their baseline body weight.

	Percent of Subjects		
	≥5% weight loss	≥10% weight loss	≥15% weight loss
Qsiva Mid dose	63%	37%	18%
Qsiva High dose	69%	47%	31%

Secondary Outcome parameters

Results are presented for the pooled 1-year cohort (i.e. studies OB-302 and OB-303) as well as for separate studies.

Waist Circumference

In the 1-year cohort, the mean change in waist circumference from baseline to Week 56 with LOCF was -3.0 cm for the placebo group, -5.1 cm for the PHEN/TPM 3.75/23 mg group, -8.4 cm for the PHEN/TPM 7.5/46 mg group, and -10.0 cm for the PHEN/TPM 15/92 mg group. For all treatment groups, the LS mean change in waist circumference from baseline was statistically significant ($p<0.0001$). The difference compared to placebo was statistically significant for all active treatment groups.

Blood Pressure

In the 1-year cohort, treatment with all three doses of PHEN/TPM resulted in statistically significant decreases in SBP relative to placebo at Week 56 with LOCF. Treatment with PHEN/TPM 15/92 mg resulted in a statistically significant decrease in DBP relative to placebo at Week 56 with LOCF.

Even though phentermine increases heart rate, this did not result in a detrimental effect with respect to blood pressure in the studied population. The reduction of systolic blood pressure in studies 301 and 303 is of clinical relevance, but may very well be secondary to weight loss.

Table 5. Changes in Systolic Blood Pressure and Diastolic Blood Pressure at Study Endpoint (LOCF) – Individual Studies OB-301, OB-302, OB-303, and OB-305 –ITT

	OB-301			OB-302			OB-303			OB-305		
		Change at Week 28 (LOCF) [1]			Change at Week 56 (LOCF) [1]			Change at Week 56 (LOCF) [2]			Change at Week 108 (LOCF) [2]	
Treatment	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value
Systolic Blood Pressure												
Placebo	103	-1.8 (1.07)	–	498	0.9 (0.58)	–	979	-2.4 (0.48)	–	227	-3.2 (0.85)	–
PHEN/TPM 3.75/23				234	-1.8 (0.79)	0.0019						
PHEN/TPM 7.5/46	102	-7.0 (1.08)	0.0004				488	-4.7 (0.63)	0.0008	153	-4.7 (1.05)	0.2441
PHEN/TPM 15/92	103	-5.2 (1.07)	0.0224	498	-2.9 (0.57)	<0.0001	980	-5.6 (0.47)	<0.0001	295	-4.3 (0.78)	0.3177
Diastolic Blood Pressure												
Placebo	103	-0.7 (0.77)	–	498	0.4 (0.40)	–	979	-2.7 (0.32)	–	227	-3.9 (0.58)	—
PHEN/TPM 3.75/23				234	-0.1 (0.55)	0.4257						
PHEN/TPM 7.5/46	102	-2.2 (0.77)	0.1724				488	-3.4 (0.42)	0.1281	153	-3.7 (0.71)	0.8830
PHEN/TPM 15/92	103	-2.0 (0.77)	0.2242	498	-1.5 (0.40)	0.0002	980	-3.8 (0.32)	0.0031	295	-3.5 (0.53)	0.5815

Lipid parameters

In the 1-year cohort, treatment with all three doses of PHEN/TPM doses resulted in statistically significant mean percent decreases in TC/HDL-C ratio relative to placebo.

Treatment with PHEN/TPM 15/92 mg and PHEN/TPM 7.5/46 mg resulted in statistically significant mean percent decreases in TG and statistically significant mean percent increases in HDL-C relative to placebo. Treatment with PHEN/TPM 15/92 mg also resulted in a statistically significant mean percent decrease in TC relative to placebo. Thus, there were no indications of a detrimental effect of PHEN/TPM on lipid parameters. On the contrary, beneficial effects were generally recorded. However, these are likely secondary to weight loss

Glucose related endpoints

As expected, weight loss had a beneficial effect on glucose and insulin parameters both in diabetic and non-diabetic subjects (see further studies in special populations). For subjects without type 2 diabetes at the time of entry into study OB-303 (n = 525), the incidence of new onset diabetes was 7.0% in the placebo group compared to 3.2% in the PHEN/TPM 7.5/46 mg group (relative risk, 0.46; 95% confidence interval [CI], 0.15-1.38) and 1.7% in the PHEN/TPM 15/92 mg group (relative risk, 0.25; 95% CI, 0.08-0.76).

Clinical studies in special populations

Results in subgroups are presented for the 1-year Phase 3 cohort that consists of all subjects who were randomised to the pivotal Phase 3 studies OB-302 and OB-303.

Gender

Both females and males experienced clinically relevant reductions of body weight with all doses of, in general, the same magnitude.

Age

The experience in subjects older than 65 years is limited, and it should be noted that subjects older than 70 years were not included in the main studies as per exclusion criteria. This is reflected in the proposed SmPC. However, based on the available information, there were no major differences seen between younger and older subjects.

Race

The majority of the subjects in the studies were non-blacks. However, based on the available information, there were no major differencesseen between black and non-black subjects.

BMI

The majority of the subjects had baseline BMI between 30 and 40 kg/m^2. There were no major differences in effect based on baseline BMI, even though the experience in subjects with BMI <30 kg kg/m^2 is limited.

Table 6 Percent Weight Loss at Week 56 With LOCF – ITT–1-Year Cohort – Subgroups of Subjects With Baseline BMI <30 kg/m^2, ≥30 kg/m^2 and <40 kg/m^2, and ≥40 kg/m^2

Treatment	N [1]	Baseline [2] Mean (SD)	Week 56 With LOCF [3] Mean (SD)	Percent Weight Loss [4]		
				Mean (SD)	LS Mean (SE)	P-value
Subjects with baseline BMI <30 kg/m^2						
Placebo	71	78.4 (8.95)	77.6 (9.84)	1.1 (4.46)	1.1 (0.75)	0.1516
PHEN/TPM 3.75/23	0					
PHEN/TPM 7.5/46	33	79.6 (9.51)	72.2 (9.04)	9.1 (6.45)	9.1 (1.10)	<0.0001
PHEN/TPM 15/92	71	80.9 (11.05)	73.7 (12.31)	9.1 (7.70)	9.1 (0.75)	<0.0001
Subjects with baseline BMI ≥30 kg/m^2 and <40 kg/m^2						
Placebo	904	100.4 (13.76)	98.5 (14.45)	1.8 (5.55)	1.9 (0.26)	<0.0001
PHEN/TPM 3.75/23	91	104.0 (12.59)	98.2 (13.77)	5.6 (7.00)	5.4 (0.80)	<0.0001
PHEN/TPM 7.5/46	344	98.9 (14.06)	90.7 (15.06)	8.3 (8.12)	8.5 (0.44)	<0.0001
PHEN/TPM 15/92	887	99.6 (13.32)	89.5 (15.35)	10.3 (8.57)	10.4 (0.27)	<0.0001
Subjects with baseline BMI ≥40 kg/m^2						
Placebo	502	124.3 (18.82)	122.1 (19.52)	1.7 (5.45)	1.7 (0.34)	<0.0001
PHEN/TPM 3.75/23	143	127.8 (21.63)	121.8 (23.15)	4.8 (6.18)	5.1 (0.67)	<0.0001
PHEN/TPM 7.5/46	111	121.5 (16.12)	111.4 (17.71)	8.4 (7.36)	8.2 (0.75)	<0.0001
PHEN/TPM 15/92	521	123.5 (17.82)	109.5 (19.65)	11.4 (9.35)	11.4 (0.33)	<0.0001

Studies in subjects with type 2 diabetes

METHODS

OB-202 was a Phase 2, randomised, double-blind, placebo-controlled, multicentre study in overweight and obese adults with type 2 diabetes, which compared phentermine and topiramate combination therapy with placebo after 28 weeks of treatment. The primary endpoint was change in HbA1c. The study population included adult subjects ≤70 years of age with a BMI ≥27 kg/m^2 and ≤45 kg/m^2 and type 2 diabetes controlled by diet or oral antidiabetic medications. Eligible subjects were assigned randomly to receive daily treatment with placebo or the combination of phentermine 15 mg and topiramate 100 mg. Phentermine was administered in the morning with breakfast, and topiramate was administered in the afternoon.

DM-230 was a 28-week extension of study OB-202, which evaluated the long-term safety and efficacy of PHEN/TPM in type 2 diabetic subjects. Subjects who completed study OB-202 and opted to participate in this extension study remained on the double-blind treatment to which they were assigned in study OB-202. During the extension study, subjects in the active treatment group received PHEN/TPM 15/92 mg capsules instead of the phentermine 15 mg capsules and topiramate 100 mg capsules administered separately in study OB-202.

DM-231 was designed as a 58-week, open-label extension of study DM-230 to evaluate the long-term safety and efficacy of phentermine/topiramate in type 2 diabetic subjects. Subjects who completed study DM-230 and opted to participate in this extension study were treated with open-label PHEN/TPM 15/92 mg capsules. Subjects underwent a 4-week titration to reach the target dose of PHEN/TPM 15/92 mg. The extension study was terminated early after 16 weeks based on input from the FDA that an open-label study would not be easily interpretable due to lack of a control group. The early termination was unrelated to safety or efficacy concerns.

RESULTS

In total, 210 subjects were randomly assigned to treatment in study 202 out of which 165 (79%) subjects completed the study. The majority of subjects were female (68%) and Caucasian (86%). The mean age of subjects was 49.4 years. At baseline, mean weight was 96.4 kg, mean BMI was 35.2 kg/m^2, and mean waist circumference was 109.9 cm. The LS mean percent weight loss at Week 28 with LOCF for the ITT Population was 1.2% for the placebo group and 8.0% for the phentermine 15 mg and topiramate 100 mg group ($p<0.0001$). The percentage of subjects with ≥5% weight loss at Week 28 with LOCF for the ITT population was 14% with placebo and 61% with phentermine 15 mg and topiramate 100 mg treatment ($p<0.0001$).

The LS mean change in HbA_{1c} from baseline to Week 28 with LOCF for the ITT Population was -0.6% for the placebo group and -1.1% for the phentermine 15 mg and topiramate 100 mg group ($p<0.0001$). The LS mean change in fasting blood glucose from baseline to Week 28 with LOCF for the

ITT Population was -7.6 mg/dL for the placebo group and -32.6 mg/dL for the phentermine 15 mg and topiramate 100 mg group ($p=0.0001$).

Of the 210 subjects enrolled in study OB-202, 130 (61.9%) subjects continued into study DM-230. In total, 120 (92.3%) subjects completed the study.

The percentage of subjects with ≥5% weight loss from Week 0 to Week 56 with LOCF for the ITT Population was 24% with placebo and 65% with PHEN/TPM 15/92 mg treatment ($p<0.0001$).The LS mean percent weight loss from Week 0 (start of study OB-202) to Week 56 with LOCF for the ITT Population was 2.7% for the placebo group and 9.4% for the PHEN/TPM 15/92 mg group ($p<0.0001$).

The LS mean change in HbA_{1c} from Week 0 to Week 56 with LOCF for the ITT Population was -1.2% for the placebo group and -1.6% for the PHEN/TPM 15/92 mg group ($p=0.0381$).

The degree of weight loss in these studies was clearly of clinical significance. However, the quite impressive reduction in HbA1c in the placebo group indicates that subjects were not on optimal antidiabetic treatment during study OB-202 and when entering study DM-230.

Of the 120 subjects who completed study DM-230, 101 subjects continued into study DM-231. The mean percent weight loss from Week 0 (the start of study OB-202) to Week 72 was 8.4% for the 16-week Population and 10.1% for the 72-week Population.

Supportive studies

OB-201 was a Phase 2, randomised, double-blind, placebo-controlled, single-centre study in obese adults, which compared phentermine and topiramate combination therapy with placebo and the single-agent phentermine and topiramate components after 24 weeks of treatment. The primary endpoint was percent weight loss. The study population included adult subjects ≤60 years of age with a BMI ≥30 kg/m^2 and ≤50 kg/m^2. Eligible subjects were assigned randomly to receive daily treatment with placebo, phentermine 15 mg, topiramate 100 mg, or the combination of phentermine 15 mg and topiramate 100 mg.

In total, 200 subjects were randomly assigned to treatment. Of the 200 subjects, 158 (79.0%) subjects completed the study to Week 24. The LS mean percent weight loss at Week 24 with LOCF for the ITT Population was 2.1% for the placebo group, 4.6% for the phentermine 15 mg group, 6.3% for the topiramate 100 mg group, and 10.7% for the phentermine 15 mg and topiramate 100 mg group.

Treatment with phentermine 15 mg and topiramate 100 mg resulted in a significantly greater percent weight loss than phentermine 15 mg monotherapy ($p<0.0001$), topiramate 100 mg monotherapy ($p<0.0001$), and placebo ($p<0.0001$).

OB-204 was a Phase 2, randomised, double-blind, placebo-controlled, parallel-group, single-centre study in obese adults with moderate to severe obstructive sleep apnoea, which compared full-dose PHEN/TPM with placebo after 28 weeks of treatment. The primary endpoint was the change in apnoea/hypopnoea index (AHI) as measured by overnight polysomnography in a sleep laboratory. Weight loss was assessed as a secondary efficacy variable. The study population included adult subjects ≥30 years and ≤65 years of age with a BMI ≥30 kg/m^2 and ≤40 kg/m^2 with obstructive sleep apnoea/hypopnoea syndrome who had not been treated with Continuous Positive Airway Pressure (CPAP) or who were not compliant with CPAP use within the 3 months prior to screening. Eligible subjects were assigned randomly to receive daily treatment with placebo or PHEN/TPM 15/92 mg capsules.

In total, 45 subjects were randomly assigned to treatment. Of the 45 subjects, 40 (88.9%) subjects completed the study to Week 28. The LS mean percent weight loss at Week 28 with LOCF for the ITT Set was 4.2% for the placebo group and 10.3% for the PHEN/TPM 15/92 mg group($p=0.0006$). The LS mean change in AHI from baseline to Week 28 with LOCF was -16.6 for the placebo group and -31.5 for the PHEN/TPM 15/92 mg group ($p= 0.0084$).

2.5.3. Discussion on clinical efficacy

Obesity is a chronic clinical condition that usually requires long-term therapy to induce and maintain weight loss and is associated with increases in both morbidity (hypertension, dyslipidaemia, insulin resistance and type 2 diabetes mellitus, cardiovascular disease, musculo skeletal problems, infertility) and mortality.

Non-pharmacological treatment options (nutritional education, behaviour modification and increased activity and exercise) should always be first-line therapy. However, compliance to these treatment options is sometimes disappointing, and in such situations pharmacological treatment may be of value as an adjunct to dietary measures and physical exercise. Currently, available pharmacological options in the EU are restricted to drugs that inhibit the absorption of nutrients from the gastro-intestinal tract.

In severe obesity, very low calorie diets may be applied for a limited period of time. Additionally, surgery may be an alternative as a last resort. Although no studies have as yet confirmed an effect on mortality or morbidity, weight reduction has been associated with reduction in blood pressure in both normotensive and hypertensive individuals, improvement in lipid profiles and improved glycaemic

control in both subjects without diabetes and subjects with type 2 diabetes. Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight.

In the current application, the Applicant presents the results from four phase 3 studies (OB-301, 302, 303 and 305) and five phase 2 studies to support the efficacy associated with PHEN/TPM.

The duration of the studies were 28 and 56 weeks, while subjects included in study 305 which was an extension to study 303, were followed for a total of 108 weeks. Both subjects with and without weight-related co-morbidities were studied. However, the experience in subjects older than 70 years and subjects with cardiac disorders is limited.

All studies supported a clinically and statistically relevant weight reducing effect of the 7.5/46 mg and the 15/92 mg dose. Mean percentage weight loss from baseline was approximately 8 and 10 % for the 7.5/46 mg and 15/92 mg dose, respectively. Approximately, 62 and 67 % reached at least 5% weight loss and 38% and 45% reached 10% weight loss, with the two doses, respectively. Weight reduction was similar and independent from gender, co-morbidities and BMI. The additive effect of the top over the mid dose was limited in one of the studies, but seems to be more pronounced in subjects with high baseline BMI. The Applicant therefore proposed during the assessment of the application to limit the use of the high dose to these subjects.

Concerning secondary efficacy endpoints, reductions of waist circumference, blood pressure and lipid parameters were seen in most treatment groups. There were also minor reductions in glucose and insulin parameters. Thus, from the outcomes of these secondary efficacy endpoints there were no indications that treatment with PHEN/TPM would have a detrimental effect on cardiovascular risk factors. On the contrary, beneficial effects were generally recorded, albeit the benefit for blood pressure was not significant any longer after 2 years. However, these were likely secondary to weight loss.

Long term data was considered to be limited by CHMP. The results between week 56 and 108 in study 305 show that there was a mean weight gain in all groups, most pronounced in the highest dose group. However, the treatment comparisons are not randomised comparisons and should be interpreted with care. The Applicant has not performed a withdrawal study, but from studies with other weight reducing agents as well as experience from clinical practise, a weight gain can be expected when treatment is withdrawn.

Information on weight development in subjects withdrawing is limited to rather few subjects. As, expected, these subjects increased their body weight post withdrawal. However, this increase seems to develop rather slowly and there is no indication of a rebound effect with an increase above baseline weight. The mid dose (7.5/46 mg) was proposed by the applicant as the recommended dose with up titration to the higher dose if needed after 6 months treatment only in subjects with BMI ≥ 35. Based on the efficacy data, showing that most of the expected weight loss is reached after 6 months as well as a clinically relevant effect of the mid dose and an incremental effect of the higher dose, this was considered as a reasonable approach from an efficacy point of view by CHMP. However, to further identify the population truly benefitting from the treatment, the CHMP requested that treatment should be stopped in subjects not achieving a clinically relevant weight reduction (< 5% weight reduction) after 3 months treatment which was agreed to by the Applicant.

2.5.4. Conclusions on the clinical efficacy

Treatment with PHEN/TPM 7.5/46 mg and 15/92 mg for 28 and 56 weeks resulted in clinically relevant reductions of body weight, with a maximum effect after approx. 36-40 weeks of treatment. The magnitude of the weight loss was larger compared to previously approved weight reducing agents and

may be, based on epidemiological data, expected to reduce the risk of CV disease. From the secondary efficacy outcome parameters there were no indications of a detrimental effect on cardiovascular risk factors, but rather beneficial effects on blood pressure, albeit not anymore significantly after 2 years, glucose and lipids, most likely secondary to weight loss. The effect was similar in subpopulations examined, but the experience in older subjects and patients with cardiovascular disease was very limited.

2.6. Clinical safety

Patient exposure

Overall mean exposure to study drug for the 1-year cohort was 286.1 days, and overall median exposure to study drug was 391.0 days. For the 2-year cohort, overall mean exposure to study drug during studies OB-303 and OB-305 was 728.5 days, and overall median exposure was 756.0 days. The majority of subjects were female and Caucasian. The mean age of subjects was 48.3 years. At baseline, mean weight was 107.1 kg, mean BMI was 38.3 kg/m^2, and mean waist circumference was 115.5 cm.

Topiramate is in use for several years, indicated for treatment of epilepsy and migraine prophylaxis. For Phentermine there is considerable exposure in the US, where it has been marketed for over 40 years as short term treatment (less than 3 months) for weight reduction.

Adverse events

3179 (82.0%) subjects in the 1-year cohort had a TEAE. The overall incidence of TEAEs was higher in the PHEN/TPM treatment groups than in the placebo group (PHEN/TPM 15/92 mg, 87.2%; PHEN/TPM 7.5/46 mg, 85.1%; PHEN/TPM 3.75/23 mg, 80.0%; placebo, 76.0%). In the 2-year cohort 637 (94.4%) subjects had a TEAE during studies OB-303 and OB-305. The overall incidence of TEAEs was 96.0% in the placebo group, 92.8% in the PHEN/TPM 7.5/46 mg group, and 93.9% in the PHEN/TPM 15/92 mg group. There doesn't seem to be any significant difference in the pattern of AEs over time comparing the two cohorts. However, the frequency of AEs increases with increased dose, and is considerably higher in the maximum dose group. The difference between placebo and the PHEN/TPM 15/92 mg group (in the 1-year cohort) is especially obvious for the nervous system disorders (9.5% vs. 34.5%), [subgroups paraesthesia (1.2% vs. 17.3%) and dysgeusia (1.0% vs. 8.5%)], the gastrointestinal disorders (10.6% vs. 31.4%), and psychiatric disorders (6.3% vs. 16.8%), [for subgroup depression (0.5% vs. 3.4%)]. Figures are similar for the 2-year cohort.

The severe drug-related TEAEs reported in ≥ 0.5% of subjects were dry mouth, headache, back pain, nephrolithiasis, and constipation. Nine severe cases of nephrolithiasis (0.6% of subjects) were reported in the dose group PHEN/TPM 15/92 mg. This AE could be related to bicarbonate decrease. See discussion on serum bicarbonate below.Paraesthesia was described in different cohorts with a rate of up to 20%, mostly seen in the highest dose group, and was also noted as a reason for study discontinuation. Paraesthesia is thought to be related to the TPM component, due to being a carbonic anhydrase inhibitor. In the 1-year cohort, the most frequently reported TEAE was paraesthesia (overall 17.0%). After drug termination, the time to resolution was approximately three months, and resolved in 75-80% of cases. This would have been reflected in the proposed SmPC.

Serious adverse event/deaths/other significant events

One subject in the 1-year cohort died; in the placebo group one patient (in study OB-303) died from cardio-respiratory arrest. The most frequently reported severe drug-related TEAE in the placebo group

was headache. The most frequently reported severe drug-related TEAE in the PHEN/TPM 7.5/46 mg group was constipation. The most frequently reported severe drug-related TEAE in the PHEN/TPM 15/92 mg group were dry mouth, headache, constipation, dysgeusia, insomnia, nephrolithiasis, dizziness, fatigue, irritability, depression, anxiety, decreased appetite, and anorexia.

Targeted adverse events

There were targeted medical events identified based on the previous knowledge of the safety profiles of the separate compounds; *cognitive disorders* (including attention, language, memory impairment, and other cognitive disorders), *drug abuse/drug withdrawal*, *psychiatric disorders* (including anxiety, depression, sleep disorders, and suicide/self injury), and *cardiac disorders* (arrhythmias, ischemic heart disease).

Cognitive disorders

The incidence of TEAEs in the **attention** subclass was 0.6% for the placebo group, 0.4% for the PHEN/TPM 3.75/23 mg group, 2.0% for the PHEN/TPM 7.5/46 mg group, and 3.5% for the PHEN/TPM 15/92 mg group.

The incidence of TEAEs in the **memory impairment** subclass was 0.6% for the placebo group, 0.8% for the PHEN/TPM 3.75/23 mg group, 1.8% for the PHEN/TPM 7.5/46 mg group, and 2.5% for the PHEN/TPM 15/92 mg group. The assessment of cognitive function was only performed in one phase III trial of insufficient duration (6 months) with a not widely recognised RBANS scale, which is considered a limitation.

Psychiatric disorders

The incidence of TEAEs in the **anxiety** subclass was 2.6% for the placebo group, 4.6% for the PHEN/TPM 3.75/23 mg group, 4.8% for the PHEN/TPM 7.5/46 mg group, and 7.9% for the PHEN/TPM 15/92 mg group (9.5% in the 2-year cohort). The rate of experiencing anxiety was higher in the Qsiva treated subjects, and most so in the full dose group. It generally occurred early, within the first 12 weeks. History of anxiety at baseline was associated with a greater risk of experiencing anxiety.

The incidence of TEAEs in the **depression** subclass was 3.4% for the placebo group, 5.0% for the PHEN/TPM 3.75/23 mg group, 3.8% for the PHEN/TPM 7.5/46 mg group, and 7.7% for the PHEN/TPM 15/92 mg group (8.1% for the 2-year cohort). Most depression TMEs were mild or moderate in severity. Of the 121 subjects in the Qsiva full dose group who experienced a depression TME, the event was considered severe in seven cases (5.8%). The incidences of depression TME events were greater in those who had a history of depression than in those who did not have a history of depression, especially in those not taking antidepressive drugs at baseline. However, the relative risk compared to placebo was not different between subjects with and without history of depression.

Table 7. Incidence of Depression TME Subclass by Antidepressant Medication Status at Baseline – 1-Year Cohort:

History of Depression (Total N), %	Placebo NM N=93 TM N=241 ND N=1227	Qsiva Low NM N=21 TM N=36 ND N=183	Qsiva Mid NM N=22 TM N=83 ND N=393	Qsiva Full NM N=93 TM N=213 ND N=1274
Hx of depression, not on meds (NM) (229)	11.8	9.5	0.0	18.3
Hx of depression, taking meds (TM) (573)	4.6	11.1	8.4	8.5
No Hx of depression (ND) (3077)	2.5	3.3	3.1	6.8

Hx=history; ND=No history of depression and not on medication; NM=Depression history but not on medication; TM=Depression history and taking medication; TME=targeted medical events

The depression TEAE led to study drug discontinuation for 35 of 152 (23.0%) subjects on PHEN/TPM and four of 53 (7.5%) subjects on placebo. In the studies there were no SAE of depression for the QSIVA-treated subjects. There was no increase in the use of new antidepressants or new anxiolytics, compared to the placebo group.

QPH-9 and C-SSRS were used to assess subjects at baseline and during treatment. Among QSIVA-treated subjects, Depression TMEs appeared to be somewhat more likely to occur in subjects with baseline PHQ-9 scores of 5 – 9, compared to those with scores <5, particularly at the full dose of QSIVA. Likewise, the incidence of depression TMEs appeared greater in those who reported suicidal ideation at baseline. Thus, QPH-9 and C-SSRS appeared to identify subjects at baseline who were at risk for experiencing depression later on during treatment with QSIVA. This was however not evident for suicidal ideation.

Most events occurred within week 12. The incidences of depression TMEs were 2.2%, 2.6%, and 3.7% in the placebo, mid- and full dose QSIVA groups respectively during the second year of treatment. , Depressions occurring in the QSIVA full dose group had the shortest time to onset (median time 44 days for the full dose compared to 75 days for placebo). Time for resolution of events was (median) 7 days after discontinuation of drug; and 16 days after dose reduction.

Most events resolved without stopping study drug, including approximately 75% in the mid- and full-dose QSIVA groups.

No episodes of suicidal behaviour or suicide were recorded. However, there were two incidences of suicidal ideation; one in the placebo group of study OB-303 (drug discontinued and subject withdrawn from study and recovered from the event), and one in the PHEN/TPM 3.75/23 mg group in study OB-302 (drug discontinued and subject withdrawn from study and recovered from the event).

4.1% of subjects were excluded in the phase III trials because of psychiatric illness. However, of the randomised subjects; 4% had suicidal ideation, 21% had a history of depression, and 12% had a history of anxiety.

The incidence of TEAEs in the **sleep disorders** subclass was 5.7% for the placebo group, 6.7% for the PHEN/TPM 3.75/23 mg group, 6.8% for the PHEN/TPM 7.5/46 mg group, and 10.8% for the PHEN/TPM 15/92 mg group (12.9% in the 2-year cohort). Sleep disorders TME was most experienced with the full dose group, and as with anxiety it occurred early in treatment. There were no SAEs during the trials.

Cognitive and psychiatric disorders were both identified risks in the RMP which had been proposed by the applicant

Cardiac disorders

Increase in heart rate/CV Safety

The incidence of TEAEs in the cardiac arrhythmia subclass was 1.8% for the placebo group, 1.3% for the PHEN/TPM 3.75/23 mg group, 4.2% for the PHEN/TPM 7.5/46 mg group, and 4.7% for the PHEN/TPM 15/92 mg group (4.1% in the 2-year cohort). Most common were palpitations (1.8% and 0.8% in the PHEN/TPM and placebo groups, respectively) and increased heart rate (0.6% and 0.1% in the PHEN/TPM and placebo groups, respectively.) The mean change from baseline to Week 108 in heart rate was 0.4 bpm for the placebo group, 1.3 bpm for the PHEN/TPM 7.5/46 mg group, and 1.7 bpm for the PHEN/TPM 15/92 mg group. The cardiac arrhythmia TEAE led to study drug discontinuation for 15 of 98 (15.3%) subjects on PHEN/TPM and six of 28 (21.4%) subjects on placebo.

The mechanism of action of phentermine is primarily mediated by the central actions of releasing catecholamine in the hypothalamus involving beta adrenergic and dopamine receptors. Thus, a secondary effect on heart rate (HR) and blood pressure can be expected. The Applicant´s argument that there is no evidence that a drug which increases HR by 1-2 beats per minute on the background of reduced blood pressure causes CV harm was acknowledged. However, a larger proportion of subjects treated with QSIVA had an increase in heart rate > 10 bpm from baseline at any time point compared to placebo. Further, the incidence of treatment emergent adverse events (TEAEs) in the cardiac arrhythmia subclass was higher in the full-dose group (4.7%) and mid-dose group (4.2%) than in the placebo group (1.8%). Thus, there were individuals who had a considerably larger effect on heart rate than what was reflected by the mean increase. However, observed changes in heart rate occurred primarily in subjects with a low (<60) baseline HR, thus not resulting in very high pulse rates. The Applicant has analysed the change in systolic blood pressure as a function of change in heart rate in the 1-Year cohort. The results show that subjects with categorical increases in HR still demonstrated reductions in blood pressure compared to placebo.

The overall clinical program included subjects with hypertension (40%), dyslipidaemia (26%), and diabetes (14%) at baseline. There were approx. 500 subjects (~15% of the total patient population) in the high risk category defined as subjects with a history of CAD, PAD, stroke or subjects with diabetes mellitus and ≥1 CVD risk factors (hypertension or dyslipidaemia). The vast majority of subjects in the high risk group were subjects with diabetes.

The Applicant has performed an assessment of the CV safety profile of Qsiva with respect to major cardiovascular events, and the results showed no increase in CV risk (OR, 0.49; 95% CI, 0.19-1.25) in the entire population studied. Subjects with higher CV risk such as men and older women (age>55) receiving Qsiva also showed no increased CV risk (OR, 0.36, 95% CI, 0.12-1.06).

However, the results of these analyses must be interpreted with caution considering that the annual incidence rates were very low (11 events in the PHEN/TPM group consisting of 2581 subjects, incidence

rate 0.3, 10 events in placebo group, incidence rate 0.6). Further, the definition of cardiovascular events was rather broad (cardiovascular death, myocardial infarction, stroke, coronary revascularization, unstable angina, and congestive heart failure). For CV deaths, myocardial infarction and stroke 12 events have been recorded in 4323 patients, HR= 0.84, 95% CI [0.26; 2.64], representing an incidence rate of 0.3%, six of which were myocardial infarctions in the PHEN/TPM group versus 0 in the placebo group.

This indicates that the population studied was not at a very high risk of CV events. A study in a more high risk population is planned by the applicant.

Increased heart rate is an identified risk in the RMP which had been proposed by the applicant.

Pulmonary hypertension and valvulopathy

Cases of primary pulmonary hypertension and valvulopathy have been reported when phentermine was used in combination with fenfluramine. Fenfluramine was identified to have an activity for 5HT2b on cardiac valve whereas neither phentermine nor topiramate have 5HT2b activity.

However, some cases of valvulopathy were reported with phentermine alone: a case of mild mitral and severe aortic regurgitation has been reported in 2006 in a 28 year-old woman with apparently no other risk factor than a 8-month phentermine use (Yosefy et al, Int J Cardiol 2006;106;262-3). A case of pulmonary hypertension and tricuspid regurgitation in a 29-year woman with no other risk factors than 5-week use of phentermine (37.5 mg daily) was also reported recently (Bang et al, Yonsei Med J 51(6):971-973, 2010).

In addition, a 39-year-old woman with SAE of atrial fibrillation in study OB-302 treated with full dose PHEN/TPM during 87 days was explored by an echocardiogram. Mild, mitral regurgitation was found, not known before the study.

A phase 2 proof-of-concept study on echocardiogram investigation with an echocardiogram performed at baseline and at the end of the study, was performed by the applicant. The study duration of only 6 months was not sufficient and thus, no conclusion can be drawn on valvular heart abnormalities from these data. However, the CHMP's Cardiovascular Working Party concluded that regarding valvular disorders phentermine has been found not to be linked to those events.

Valvulopathy and primary pulmonary hypertension were included as potential risks in the RMP which had been proposed by the applicant.

Laboratory findings

All of the treatment groups had mean decreases in alanine transaminase (ALT) and alkaline phosphatase from baseline; the mean decreases in ALT were numerically larger for the PHEN/TPM 15/92 mg group and PHEN/TPM 7.5/46 mg group than for the PHEN/TPM 3.75/23 mg group and placebo group. The PHEN/TPM 15/92 mg group and PHEN/TPM 7.5/46 mg group had mean decreases in aspartate transaminase (AST) from baseline, while the PHEN/TPM 3.75/23 mg group and placebo group had mean increases in AST.

The PHEN/TPM treatment groups had a mean decrease in serum bicarbonate from baseline, while the placebo group had a small mean increase in serum bicarbonate. Dose-related increases in the percentage of subjects with serum bicarbonate <21 mEq/L at any time were observed: 92 (5.9%) subjects in the placebo group, 39 (16.3%) subjects in the PHEN/TPM 3.75/23 mg group, 112 (22.5%) subjects in the PHEN/TPM 7.5/46 mg group, and 474 (30.0%) subjects in the PHEN/TPM 15/92 mg group. The percentage of subjects with serum bicarbonate <17 mEq/L was low overall, but higher in the PHEN/TPM groups than in the placebo group: 4 (0.3%) subjects in the placebo group, 4 (1.7%)

subjects in the PHEN/TPM 3.75/23 mg group, 8 (1.6%) subjects in the PHEN/TPM 7.5/46 mg group, and 31 (2.0%) subjects in the PHEN/TPM 15/92 mg group. In the 2-year cohort, 72 (10.7%) subjects had a decrease in serum bicarbonate from baseline >5 mEq/L at two consecutive visits or at their last study visit: four (1.8%) subjects in the placebo group, 20 (13.1%) subjects in the PHEN/TPM 7.5/46 mg group, and 48 (16.3%) subjects in the PHEN/TPM 15/92 mg group. Six (3.9%) subjects in the PHEN/TPM 7.5/46 mg group and 20 (6.8%) subjects in the PHEN/TPM 15/92 mg group had a serum bicarbonate level <21 mEq/L at two consecutive visits during studies OB-303 and OB-305 or at their last study visit. One (0.3%) subject in the PHEN/TPM 15/92 mg group had a serum bicarbonate level <17 mEq/L at two consecutive visits during studies OB-303 and OB-305 or at the last study visit.

In the trials this generally occurred early in treatment, with a peek reduction at week 4. The values below the lower limit of the normal range increased in a dose-dependent way.

There was no additional risk seen for subjects on metformin, when looking at subgroups taking / not taking metformin. No AEs regarding bone density was found.

Only <1% had serum bicarbonate below 17 mEq/L. No difference was shown if on metformin or not. The values seem to fluctuate in many of the cases, without any change in study drug. The recommendation of periodic assessments of serum bicarbonate is reflected in the RMP which had been proposed by the applicant.

Otherwise, no clinically important differences among the treatment groups in mean changes in safety laboratory parameters were noted.

Vital signs

Mean decreases in SBP and DBP were observed for all of the treatment groups. The mean decreases in SBP were larger for the PHEN/TPM groups than for the placebo group. The mean decreases in DBP were larger for the PHEN/TPM 15/92 mg group and PHEN/TPM 7.5/46 mg group than for the placebo group. There were a higher proportion of subjects with increased heat rate on the PHEN/TPM groups compared to placebo. In the safety set of the 1-year cohort, the mean increase (SD) was 1.3 (10.32), 0.6 (10.18), and 1.6 (10.28) for the treatment groups PHEN/TPM 3.75/23, PHEN/TPM 7.5/46, and PHEN/TPM 15/92, respectively [placebo 0.0 (10.59)].

The mean change from baseline to Week 108 in heart rate was 0.4 bpm for the placebo group, 1.3 bpm for the PHEN/TPM 7.5/46 mg group, and 1.7 bpm for the PHEN/TPM 15/92 mg group. The proportions of subjects with an increase in heart rate > 10 bpm from baseline at any time point during the studies were 42 % in the placebo group compared to 50.4% and 56.1% in the mid and high dose groups, respectively. The proportions in the 2 year cohort were 55.9, 63.4, and 71.5%, respectively.

Table 8. Summary of Categorical Increases in Blood Pressure (mm Hg) and Heart Rate (bpm) from Baseline – 2 year cohort

Parameter Category	Placebo (N=227) n (%)	PHEN/TPM 7.5/46 (N=153) n (%)	PHEN/TPM 15/92 (N=295) n (%)
Systolic blood pressure			
>5 mmHg	186 (81.9)	111 (72.5)	204 (69.2)
>10 mmHg	145 (63.9)	82 (53.6)	163 (55.3)
>15 mmHg	108 (47.6)	57 (37.3)	114 (38.6)
>20 mmHg	63 (27.8)	33 (21.6)	60 (20.3)
>25 mmHg	41 (18.1)	21 (13.7)	37 (12.5)
>30 mmHg	23 (10.1)	11 (7.2)	19 (6.4)
Diastolic blood pressure			
>5 mmHg	154 (67.8)	102 (66.7)	194 (65.8)
>10 mmHg	84 (37.0)	50 (32.7)	109 (36.9)
>15 mmHg	50 (22.0)	28 (18.3)	54 (18.3)
>20 mmHg	25 (11.0)	11 (7.2)	15 (5.1)
Heart rate			
>5 bpm	185 (81.5)	132 (86.3)	257 (87.1)
>10 bpm	127 (55.9)	97 (63.4)	211 (71.5)
>15 bpm	90 (39.6)	64 (41.8)	143 (48.5)
>20 bpm	49 (21.6)	26 (17.0)	76 (25.8)

Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.
All measurements taken during the randomised, double-blind treatment period of studies OB-303 and OB-305 were considered.
PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate.

Increased heart rate is noted as a potential risk in the RMP which had been proposed by the applicant.

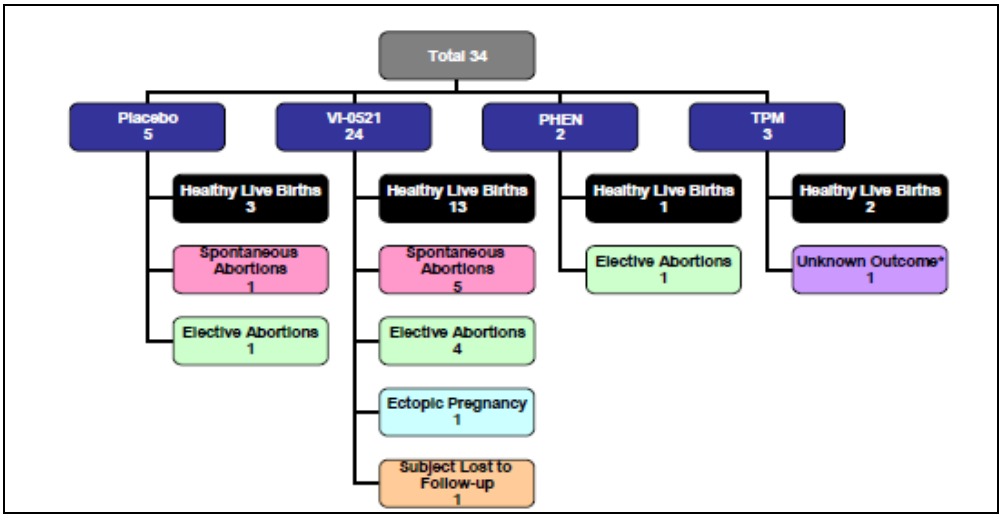
Safety in special populations

In general, in study OB-303 (including subjects with co-morbidities), the most common conditions were hypertension, dyslipidaemia and impaired glucose tolerance. Most subjects had increased waist circumference. Approx. 16% of the subjects had diabetes. For other co-morbidities, 17% of the subjects had a history of depression while only 1.1 % of the subjects had a history of coronary artery disease.

Gender: For the targeted medical events, there was a slight difference in the cognitive disorders subclasses of memory impairment and language (more females than males). Age: The subgroup of subjects ≥65 years of age was relatively small: 98 subjects in the placebo group, four subjects in the PHEN/TPM 3.75/23 mg group, 47 subjects in the PHEN/TPM 7.5/46 mg group, and 105 subjects in the PHEN/TPM 15/92 mg group, which makes evaluation difficult. The overall incidences of TEAEs and drug-related TEAEs were marginally higher for subjects ≥65 years of age than for subjects <65 years of age across the treatment groups; for the 15/92 mg treatment groups 93.3% and 86.7% respectively. No significant difference was found with race. The incidences of SAEs in subjects with baseline BMI ≥40 kg/m^2 were higher than in subjects with baseline BMI ≥30 kg/m^2 and <40 kg/m^2 across all treatment groups, including placebo. No important differences between the baseline BMI subgroups in the incidence of adverse events with PHEN/TPM treatment that resulted in study drug discontinuation were observed. The incidences of SAEs among subjects with diabetes at baseline and subjects without diabetes at baseline were rather similar across treatment groups. No important differences between the baseline diabetic subgroups in the incidence of adverse events with PHEN/TPM treatment that resulted in study drug discontinuation were observed.

During the course of the development program, women of childbearing potential were eligible to enrol in the clinical studies. Women of childbearing potential underwent informed consent discussions prior to study entry regarding potential risks of pregnancy while on study drug and were eligible for participation if they agreed to use double-barrier contraception or stable hormonal contraception plus a single-barrier method, or had a tubal ligation in place. Throughout the development program, there were 34 pregnancies. One pregnancy occurred in a Phase I study, two pregnancies occurred in Phase II studies, and 31 pregnancies occurred in Phase III studies, with the following outcome:

Fig. 5: Outcome of 34 pregnancies in the clinical study program:



Drug abuse

The risk of drug abuse has to be considered. The statement of the Applicant, that abuse will be hampered by the fact that high doses of topiramate will give unpleasant adverse reactions, is acknowledged. However, phentermine has an abuse potential that cannot be overlooked. Phentermine has been listed (United Nations Convention on Psychotropic Substances) as a substance presenting a risk of abuse, posing a threat to public health. The structural pharmacological and neurochemical profile of phentermine are similar to that of amphetamine. No specific study has been performed to adequately assess drug abuse with phentermine monotherapy or combined with topiramate. It is noted in the proposed RMP as a potential risk.

Safety related to drug-drug interactions and other interactions

Study OB-108 was a drug-drug interaction study between PHEN/TPM 15/92 mg and oral contraceptives in healthy female subjects. The mean maximum ethinyl oestradiol exposure, as measured by C_{max}, was not altered when oral contraceptive was co-administered with the combination product; however, overall extent of ethinyl oestradiol exposure ($AUC_{0\text{-}inf}$) was 16% lower when oral contraceptive was co-administered. The mean maximum and overall extent of norethindrone exposure, as measured by C_{max} and $AUC_{0\text{-}inf}$, were 22% and 16% higher, respectively, when oral contraceptive was administered.

Carbonic anhydrase inhibitors, such as topiramate and acetazolamide, increase the exposure of phentermine. Alcohol accelerates the release of topiramate and the recommendation is not to combine Qsiva with alcohol. Inhibition of intestinal CYP3A4 by phentermine is possible, given available in vitro data. This has not been further investigated in vitro or followed up in vivo. At time of opinion, the CHMP recommended the applicant should provide in vitro data on the inhibition of p-gp by phentermine and in vitro data on the potential for inhibition of CYP3A4 by phentermine in the

intestines using a concentration as high as the possible intestinal concentration with the highest dose. Depending on the results in each case, it may have been necessary to perform in vivo interaction study subsequently.

During the assessment, the applicant also agreed to the need to provide in vitro data on the potential for phentermine being a substrate of renal proximal tubule (active secretion) transporters, which was recommended by CHMP.

Discontinuation due to adverse events

In total, 494 (12.7%) subjects discontinued the study medication due to an adverse event. The percentage of subjects who discontinued study drug due to an adverse event was higher in the PHEN/TPM groups than in the placebo group (PHEN/TPM 15/92 mg, 17.5%; PHEN/TPM 7.5/46 mg, 11.6%; PHEN/TPM 3.75/23 mg, 11.7%; placebo, 8.5%). In total, 353 (9.1%) subjects discontinued study drug due to a drug-related TEAE. The percentage of subjects who discontinued study drug due to a drug-related TEAE was higher in the PHEN/TPM groups than in the placebo group (PHEN/TPM 15/92 mg, 13.3%; PHEN/TPM 7.5/46 mg, 8.4%; PHEN/TPM 3.75/23 mg, 7.9%; placebo, 5.3%). The most frequent TEAEs that were reported were blurred vision and headache (low dose), dizziness and paraesthesia (mid dose) and insomnia, depression, irritability, and anxiety (high dose).

Post marketing experience

No date from post-marketing experience is currently available.

2.6.1. Discussion on clinical safety

The safety analyses were performed on data obtained from four pivotal Phase III studies (OB-301, OB-302, OB-303, and OB-305) and two supportive Phase II studies (OB-202 and DM-230). A 1-year analysis cohort has been analysed from these studies, as well as a 6-months and an all subjects cohort. The similarity between these cohorts has led to the 1-year cohort being the one presented.

A fourth analysis cohort, the 2-year cohort, was also presented. These results come from subjects from study OB-303 who entered OB-305 (one-year extension study).

Demographic and baseline characteristics of the 2-year, 6-month, and all subjects' cohorts were overall similar to those for the 1-year cohort. The exposure for the 1-year cohort as well as the 2-year cohort is divided among treatment groups, and a majority has received the maximum dose of 15/92 mg. There was, however, limited data for subjects with a history of CV disease, and this is expected to be further evaluated in a planned CV outcome study of the applicant.

There was no significant difference in the pattern of AEs over time comparing the 1-year cohort with the 2-year cohort. However, the frequency of AEs increases with increased dose, and is considerably higher in the maximum dose group. The difference between placebo and the PHEN/TPM 15/92 mg group (in the 1-year cohort) is especially obvious for the nervous system disorders (9.5% vs. 34.5%), [subgroups paraesthesia (1.2% vs. 17.3%) and dysgeusia (1.0% vs. 8.5%)], the gastrointestinal disorders (10.6% vs. 31.4%), and psychiatric disorders (6.3% vs. 16.8%), [for subgroup depression (0.5% vs. 3.4%)]. Figures are similar for the 2-year cohort.

There is overall a marked higher incidence of adverse events in the highest dose group, especially for depression, anxiety, and sleep disorders. For anxiety, this AE led to drug discontinuation for 25% of subjects on active treatment and 14.6% for subjects on placebo. Drug discontinuation because of depression was 23% for subjects in PHEN/TPM vs. 7.5% of those on placebo.

Subjects treated with Qsiva should be observed closely for signs/symptoms of depression. The applicant proposed this to be reflected in the SmPC and in the proposed medication guides. However, in the view of the CHMP these measures would not address this identified risk as the psychiatric side effects of Qsiva are not preventable and their occurrence with the use of Qsiva in the real-life situation remains uncertain.

A beneficial effect was seen for systolic and diastolic blood pressure, which could be in part due to the weight reduction. Increased heart rate occurs, and was proposed to be reflected as an identified risk in the Risk Management Plan, as this could constitute a concern, particularly for subjects with a history of CV disease. The mean change from baseline to Week 108 in heart rate was 0.4 bpm for the placebo group, 1.3 bpm for the PHEN/TPM 7.5/46 mg group, and 1.7 bpm for the PHEN/TPM 15/92 mg group. The proportions of subjects with an increase in heart rate > 10bpm from baseline at any time point during the studies were 42 % in the placebo group compared to 50.4% and 56.1% in the mid and high dose groups, respectively. The Applicant has analysed change in systolic blood pressure as a function of change in heart rate in the 1-Year cohort. The results showed that subjects with categorical increases in HR still demonstrated reductions in BP compared to placebo. However, the experience in high risk populations is limited. A CV outcome study in a more high risk population is planned by the applicant and an interim analysis is foreseen after 120 events to allow exclusion of the upper bound of the 95% confidence interval >2.0 .

In the USA, phentermine has only been indicated as a short-term adjunct for a few weeks (recommended 3-6 weeks). The product information specifies that cardiovascular disease as well as moderate to severe hypertension is contraindicated. Primary pulmonary hypertension (PPH) and/or regurgitant cardiac valvular disease, palpitation, tachycardia, elevation of blood pressure are mentioned as adverse reactions. There is extremely limited recent data from use of PHEN in the EU, whereas PHEN has been used in the USA for over 40 years, at a dose of 37.5 mg. The use has been associated with insomnia, irritability, headache, dry mouth, constipation, euphoria, increased heart rate and blood pressure, and psychosis. Long-term effects on obese patients for a period of eight years showed no association with increased blood pressure or heart rate. Dry mouth and insomnia were reported, no arrhythmias. Publications concerning valvulopathy and PPH seem to indicate an association with fenfluramine, previously used together with PHEN.

The possibility of an association between PPH and valvular cardiac disease and the use of phentermine alone and not only in combination with fenfluramine and dexfenfluramine cannot be ruled out entirely; there have been rare cases of PPH and valvulopathy in subjects who reportedly have taken phentermine alone. A phase 2 proof-of-concept study on echocardiogram investigation with an echocardiogram performed at baseline and at the end of the study was performed by the applicant. The study duration of only 6 months was not sufficient and thus, no conclusion can be drawn on valvular heart abnormalities from these data. From a mechanistic point of view the risk is considered as low as phentermine has a very low affinity for serotonin receptors, and the CHMP's Cardiovascular Working Party concluded that regarding valvular disorders phentermine has been found not to be linked to those events; the Working Party concluded also that an involvement of phentermine use in the development of PPH appears very unlikely.

Decrease in serum bicarbonate levels frequently reported in the PHEN/TPM treatment groups are of concern in the targeted population, and a recommendation of periodic assessments of serum bicarbonate was included in the proposed RMP. The issues of decrease in serum bicarbonate, metabolic acidosis, and nephrolithiasis were all proposed to be reflected in the SmPC.

As for teratogenic risk / pregnancies the risk of teratogenicity is a concern due to the known teratogenicity of topiramate. Therefore, during the procedure it was agreed that this would need to be reflected in an updated section 4.4 of the SmPC and the applicant proposed a statement as follows:

"QSIVA is contraindicated in women of childbearing potential if two methods of contraception are not being used reliably before and throughout the treatment duration (see Sections 4.3 and 4.6). Treatment with QSIVA should only be started in a female patient of childbearing potential if each of the following conditions is met: She is informed by her physician of the hazards of becoming pregnant during treatment with QSIVA; She is willing to comply with the mandatory effective contraception measures and to use two forms of a reliable contraception method without interruption during treatment with QSIVA; and She is informed by her physician of the need to immediately discontinue taking QSIVA and seek advice from the physician if she misses a menstrual period. Females who have irregular periods or amenorrhoea or who, in the opinion of the physician, may not reliably use contraception should have a pregnancy test performed at monthly intervals during treatment with QSIVA. Patients should be advised to notify their physician and discontinue treatment with QSIVA immediately if they plan to become pregnant."

The teratogenic risk was noted in the proposed Risk Management Plan as an identified risk, and risk minimisation activities (e.g. medication guides, post approval studies) were proposed by the applicant in order to avoid pregnancies in subjects taking the product. Regarding subjects with renal impairment: when comparing diabetic subjects with non-diabetic subjects, there were no clear differences in AEs and SAEs. However there was a slight difference in the frequency of drug discontinuation being higher for the group without diabetes at baseline. For the targeted medical events; there were a slightly higher number of subjects with diabetes at baseline having the following AEs: memory impairment, ophthalmic disorders; possibly reflecting issues of the diabetic population. For subjects with moderate to severe renal dysfunction the dose of 7.5/46 mg would have been the maximum dose recommended according to the applicant´s proposal. The dose titration in subjects with moderate and severe renal impairment has been questioned during the procedure by CHMP. The possibility of an every other day posology had not been considered by the applicant.

Given that the normal dose of PHEN in most subjects will be 7.5 mg and that undesirable effects are dose dependent, and the exposure observed in subjects with severe renal impairment at a dose of 3.75 mg corresponds to a dose of 11.25 mg in the normal population according to the estimation, the maintenance dose in subjects with severe renal impairment (creatinine clearance 15-30 ml/min) would have been recommended to be 3.75 mg.

Severe hepatic impairment has not been studied. In mild to moderate hepatic function the recommended maximum dose would have been 7.5/46 mg, with the possibility to increase dose if the benefit is judged to outweigh the risk (physician's discretion). Further simulations performed during the assessment indicated that there would have been likely not a need for changes in the titration regimen in subjects with mild and moderate hepatic impairment.

The risk of drug abuse cannot be overlooked. The Applicant argued that abuse will be hampered by the fact that high doses of topiramate will give unpleasant adverse reactions. However, the CHMP was of the view that phentermine has an abuse potential that cannot be disregarded. This was considered in the proposed Risk Management Plan as a potential risk, and would have been addressed in section 4.4 of the proposed SmPC.

The lower exposure of oestrogens could cause disturbances in the bleeding pattern for subjects taking oral combined contraceptives together with Qsiva, even though the increased exposure of norethindrone may contribute against an increased risk of pregnancies. Nevertheless, CHMP considered this necessary to be addressed in the SmPC, and it would have been stated in the proposed section 4.5 of the SmPC that "The possibility of decreased contraceptive efficacy should be considered in women of child-bearing potential taking Qsiva concomitantly with oral contraceptive products containing oestrogens".

2.6.2. Conclusions on the clinical safety

Known adverse events with the use of phentermine are palpitations, tachycardia, elevation of blood pressure, psychosis, CNS and gastrointestinal effects and with the use of topiramate are paraesthesia, changes in taste, ocular disorders, psychiatric and cognitive disorders. Many of these adverse events were also reported with Qsiva as a fixed-dose combination of phentermine/topiramate in four pivotal Phase III studies and two supportive Phase II studies. There was a dose-dependent increase in the incidence of depression (3.8% in the mid dose group vs. 7.7% in the highest dose group, with 3.4% in the placebo group), anxiety (4.8% vs. 7.9%, respectively, with 2.6% in the placebo group), insomnia (6.8% vs. 10.8%, respectively, with 5.7% in the placebo group), paraesthesia (11.8% vs. 17.3%, respectively, with 1.2% in the placebo group) and cognitive disorders (5.0% vs. 7.6%, respectively, with 1.5% in the placebo group; mainly attention disturbances, memory impairment and language disorders). In the setting of long term use of this product in a large population, the frequency of adverse psychiatric effects and their consequences, as well as the cognitive effects, are unknown.

Phentermine as an amphetamine-like substance has a well known drug abuse potential. Topiramate is known as a teratogenic substance causing congenital malformations. Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard to the teratogenic risk of the product when used in a less controlled real life setting. Due to the inhibitory effect of topiramate on renal carbonic anhydrase, reductions in serum bicarbonate below 21 mEq/L were seen in 2.1%, 6.4% and 12.8% in the placebo, mid and high dose groups, and therefore are of concern in the targeted population.

Phentermine's mechanism of action was a concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. In the 1 year cohort the frequency of cardiac disorders (mostly palpitations and increase in heart rate) was higher in the Qsiva groups (4.2% and 4.7% in the mid dose and high dose group, respectively) compared to placebo (1.8%). The mean change from baseline to Week 108 in heart rate was also higher in the Qsiva groups (1.3 bpm and 1.7 bpm, respectively) than in the placebo group (0.4 bpm). A meta-analysis of cardiovascular events showed the population studied to be at a low risk of cardiovascular events. Even though there was no overall signal of an increased risk of cardiovascular events in the studies, the consequences of an increased heart rate in subjects with history of, or with ongoing cardiovascular disease are unknown. Therefore, the currently available cardiovascular outcome data for Qsiva was considered inconclusive and the long term cardiovascular safety of Qsiva has not been sufficiently established.

The CHMP considered that there remain a number of uncertainties concerning several safety issues, in particular psychiatric and cognitive adverse events, but also with regard to metabolic and teratogenic risks. There are also remaining concerns about the propensity of phentermine to increase HR. Although the available data do not indicate an increased risk of CV disease in the population studied, there are not sufficient data to rule out this risk, in particular data in a high risk population, resulting in concerns with regard to the long term cardiovascular safety of the product.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

The RMP as it has been proposed by the applicant is summarised as follows:

Safety concerns	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities Routine and additional
Identified Risks:		
Cognitive disorders	Routine pharmacovigilance CV Outcome Study EU Patient Registry Cognitive Function Study	Appropriate labelling. Restrict prescribing of high dose to responders with BMI $\geq$ 35 kg/m^2 after 6 months on the mid dose. Restrict prescribing to physicians experienced in the management of obesity and obesity-related co-morbidities. Prescriber/HCP Education Guide.
Psychiatric disorders	Routine pharmacovigilance CV Outcome Study EU Patient Registry	Appropriate labelling. Restrict prescribing of high dose to responders with BMI $\geq$35 kg/m^2 after 6 months on the mid dose. Restrict prescribing to physicians experienced in the management of obesity and obesity-related co-morbidities. Restrict dispensing utilising Prescriber/HCP Checklist (checklist will prompt prescribers to watch for changes in mood and signs or symptoms of depression). Distribution only to attested pharmacies. Prescriber/HCP Education Guide. Patient Education Card.
Metabolic acidosis	Routine pharmacovigilance CV Outcome Study EU Patient Registry	Appropriate labelling. Restrict prescribing to physicians experienced in the management of obesity and obesity-related co-morbidities. Prescriber/HCP Education Guide.
Teratogenicity	Routine pharmacovigilance EU Patient Registry	Appropriate labelling. Restrict dispensing utilising prescriber/HCP Checklist. Distribution only to attested pharmacies. Prescriber/HCP Education Guide. Patient Education Card.
Increased heart rate	Routine pharmacovigilance CV Outcome Study EU Patient Registry	Appropriate labelling. Prescriber/HCP Education Guide. Patient Education Card.
Sensibility disorders	Routine pharmacovigilance EU Patient Registry	Appropriate labelling.

Potential Risks:		
Drug abuse	Routine pharmacovigilance Drug utilisation study	Appropriate labelling.
Valvulopathy	Routine pharmacovigilance CV Outcome Study	None.
Pulmonary arterial hypertension	Routine pharmacovigilance CV Outcome Study	None.
Off-label use	Routine pharmacovigilance Drug utilisation study	Appropriate labelling. Restrict prescribing to physicians experienced in the management of obesity and obesity-related co-morbidities. Restrict dispensing utilising Prescriber/HCP Checklist. Distribution only to attested pharmacies. Prescriber/HCP Education Guide.
Visual disorders	Routine pharmacovigilance EU Patient Registry	Appropriate labelling.

Missing Information:		
Elderly ≥70 years	Routine pharmacovigilance EU Patient Registry	Appropriate labelling.
Use in children and adolescents	Routine pharmacovigilance EU Patient Registry Drug utilisation study	Appropriate labelling.

The identified risks have been proposed as:

- cognitive disorders
- psychiatric disorders
- metabolic acidosis
- teratogenicity
- increased heart rate
- sensibility disorders

Important potential risks as:

- drug abuse
- valvulopathy
- pulmonary arterial hypertension
- off-label use
- visual disorders

Children and adolescents were identified as missing information.

A number of studies and registries had been proposed by the applicant and would have been included in the RMP:
A CV outcomes study, an EU patient registry, an epidemiological study (FORTRESS), a drug utilisation study (DUS), and a cognitive function study (OB-407):

CV Outcomes Study: a randomised, double-blind, placebo-controlled, multicentre safety and superiority study of Qsiva in obese subjects with cardiovascular disease or multiple cardiovascular disease risk factors. The primary efficacy endpoint is the rate of first occurrence of a primary outcome event: either nonfatal MI, nonfatal stroke, or cardiovascular death as estimated by a time to event analysis, whereas the safety endpoints include adverse events, clinical laboratory data, vital signs, physical examination results, 12-lead electrocardiogram data, and standardised neuropsychiatric assessment using Patient Health Questionnaire 9-item (PHQ-9).

EU Patient Registry: The registry is a prospective observational registry to document clinical outcomes of patients treated with QSIVA in routine clinical practise. The registry would have continued until otherwise agreed between the Company and regulatory agencies. A computer-based application is foreseen to be used for entering data into the registry database, allowing for remote data entry at physician sites.

Epidemiological Study (FORTRESS): Preliminary results from the epidemiological FORTRESS study have been presented, and were included in the proposed RMP. The results were not conclusive, and considering the incidences of oral cleft malformation and other malformations, they were not reassuring as to the safety of the drug. Further results are expected, and a more complete report from the FORTRESS study was being requested, e.g. as an update to the RMP, by the CHMP at the end of the procedure.

Drug Utilisation Study (DUS): The applicant suggested to collect data for three consecutive calendar-year periods after initial product launch, with reporting of initial results anticipated in Q1 2015.

The QSIVA Drug Utilisation Study (Q-DUS) was suggested as a non-interventional, retrospective, observational cross-sectional study using existing dispensing databases in a representative sample of countries where they are available (e.g. Denmark, Sweden, Norway, Iceland and Netherlands) as an efficient way to collect post-launch, real-world QSIVA prescribing pattern data that would have provide dinformation on appropriate prescribing.

Cognitive Function Study (OB-047): Cognitive functions is planned to be included for assessment in the CV outcomes study. As AE reporting may not be sufficient, study OB-407 was proposed by the applicant as double-blind, parallel, placebo controlled study with six months treatment duration. It would have assessed, among other items, verbal fluency, attention, reading speed/processing speed/attention, visuospatial memory, and reaction time/vigilance. A synopsis has been submitted, and was deemed acceptable by CHMP. A complete protocol would however have been requested before study start.

Medication guides for prescribers and patients have been proposed by the applicant. During the procedure the HCP medication guide has been redesigned and rewritten as a Prescriber/HCP educational guide, which has been expanded to include a summary of the risk minimisation programme. The applicant also proposed an additional Prescriber/HCP checklist tool, which focuses on the key risks mentioned in the checklist, accessible directly as a web link, downloadable as a complete pdf document, or as a hard copy by contacting the Medical Information department of the MAH. The patient medication guide has been made more concise and focussed by conversion to a Patient Education Card. The card was therefore considered complementary and distinctive, and no longer overlapping with the PIL. It refers to the PIL for further information. Delivery would have been intended primarily through the HCP downloading and sending the card electronically to the patient or

printing a copy of the card, following completion of the prescriber checklist. The content of the Patient Education Card would have been user tested prior to launch, as well as evaluated periodically electronically by aggregation of anonymised data (e.g. frequency of download/electronic transmission). Post-launch effectiveness would also have been assessed by knowledge, comprehension, and behaviour testing of a sample of patients by using Web based surveys.

The issue of restricted prescribing/distribution/dispensing has not been fully resolved during the procedure. The Applicant has described a system consisting of three parts in order to implement a restricted use of the product. These parts are restricted prescribing (to physicians experienced in obesity management), restricted distribution (to attested pharmacies), and restricted dispensing (in the pharmacy, using the prescriber (HCP checklist).

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) discussed at their meeting in September 2012 the restricted dispensing system proposed by the Applicant to mitigate off label use of Qsiva as well as to minimise the risks by identifying patients appropriate for treatment (taking into account the proposed RMP and the Applicant´s Response to CHMP Day 180 2nd LoOIs).
The PRAC agreed that the restricted dispensing using a Prescriber/HCP Checklist and distribution only to attested pharmacies may be useful for risk minimisation and may limit the off-label use if the restrictions can be implemented. However, some PRAC members expressed uncertainty about the feasibility of some features of the proposed restricted dispensing program which would undermine it. Furthermore, the PRAC considered that the proposed program for restricted prescription / distribution and dispensing may be disproportionate for this type of product which raise concern with regard to its effectiveness and feasibility.
The PRAC concluded that the RMP would need further assessment and changes prior to a possible Marketing Authorisation of the product to include relevant measures to address the risk of off-label use. The CHMP endorsed the views of the PRAC.

2.8. User consultation

The results of the user consultation with target patient groups on the proposed 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*.

Additional expert consultations

Following the CHMP request, a Scientific Advisory Group meeting was convened on 10 May 2012 to provide advice on the list of questions adopted by the CHMP at its January 2012 meeting.

1. The SAG is asked: Considering the observed weight reducing effect of QSIVA

1a) What is the expected benefit in the overall claimed target population with respect to both long term and short term beneficial effects (e.g. reduction of CV risk, beneficial effects on orthopaedic conditions, etc.).

Qsiva is an effective weight reducing agent at the mid and high dose, with an approximate 10% reduction in body weight in those who are able to persist with therapy.

Weight reduction brings important short-term benefits to the severely obese in terms of improved mobility, quality of life, self esteem and chances of employment. Other benefits include improvement in sleep apnoea and relief of joint pain in those with arthritis. It was therefore agreed that an agent capable of achieving meaningful weight loss, particularly for those in whom there were no other therapeutic options, would be a valuable addition to current therapy.

Another possible benefit mentioned by one expert is improvement of polycystic ovary syndrome (PCOS), where weight loss is associated with an increase in fertility. Since many of those seeking treatment for obesity are women of child-bearing age, often affected by PCOS, the attendant risks of unexpected pregnancy on Qsiva do however need to be considered.

Longer term benefits in terms of extension of healthy life span were more debatable. Considering obesity as a chronic condition, some experts found 2-year data to be somewhat limited for a chronic treatment and also would like to see weight data in patients discontinuing therapy. There is no question that weight loss by non-pharmacological means has been demonstrated to offer considerable long-term benefit in terms of diabetes, cardiovascular risk and other outcomes. Equally, successful weight loss also brings clear benefit in terms of proxy measures such as blood pressure, glycaemia, and reliance on other therapies. These changes might be expected to translate into long-term benefit in terms of cardiovascular risk.

On the other hand, long-term benefits in terms of hard endpoints (other than delayed short-term progression to a diagnosis of diabetes) have yet to be demonstrated for any pharmacological weight reducing therapy. Reasons for this lack of outcome data could include a high drop-out rate due to non-response, poor tolerance due to unwanted effects or poor adherence (amounting to 40% with Qsiva as with other agents), lack of sustained effect upon weight, and/or competing effects, given that some weight-reducing agents, such as sibutramine, may have deleterious cardiovascular effects of their own.

In sum, SAG agreed that the short term benefits to be expected from 5-10% weight loss were unequivocal. There are potentially important longer term benefits in terms of cardiovascular risk, but these remain hypothetical for pharmacological interventions until demonstrated by appropriately designed long-term prospective trials.

1b) Is it possible to define a target population for whom an expected higher benefit (to be defined i.e. weight loss, cardiovascular events, etc) could be identified, e.g. patients with a BMI ≥35kg/m², for which treatment alternatives are few.

Both short term disability and cardiovascular risk increase with increasing obesity, and SAG considered that the benefit/risk ratio of the proposed therapy was therefore increasingly favourable in the more severely obese. The quality of the evidence presented was currently not such as to justify wider use, as proposed by the MAH. There followed much discussion as to choice of cut-off. The general conclusion was that a BMI >35 could be considered appropriate, although it was also pointed out that BMI is only one among many considerations in the management of obesity, and a scoring system may be more appropriate instead of a set BMI threshold, and there was support from a minority of those present for a more flexible strategy which allowed for its use in those at lower BMI who might stand to gain increased benefit in terms of quality of life or longer-term risk. There was however a strong consensus view in favour of the more restrictive indication, with emphasis also upon the need for well-judged inclusion and exclusion criteria, particularly with regard to pre-existing neuropsychiatric morbidity.

Specific populations to consider were suggested by individual experts in comments and included patients with Prader-Willi Syndrome and patients preparing for bariatric surgery.

1c) Discuss the need for QSIVA as a treatment-alternative for patients with obesity taking into account the availability and the B/R of alternative therapies, i.e. lifestyle modifications and bariatric surgery

Alternative therapies are limited in the severely obese. Life style interventions are often unsuccessful or of modest benefit. Pharmacological options are very limited.

GLP-1 agonists have yet to prove their value in non-diabetic obesity, and are currently under consideration for this role – although not approved for this indication - and also have safety issues of their own. Most SAG experts would nonetheless consider them as a first-line option in obese people with diabetes in the future.

Bariatric surgery is an effective intervention in the severely obese, with or without diabetes, but access is limited (severely so in some regions) and surgical intervention is (in some instances) irreversible and has a number of unwanted short-term adverse effects together with uncertain longer-term consequences.

Allowing for exclusions and other treatment options, SAG felt that Qsiva might therefore be considered for 25-50% of the severely obese, with some individual variation among SAG members above and below this estimate.

However, more information is needed to guide fully effective clinical use.

2. The use of QSIVA is associated with several safety issues e.g. psychiatric adverse events, teratogenicity, cognitive impairment, risk of abuse as well as a potentially negative cardiovascular effect due to the sympathomimetic properties of phentermine.

2a) Discuss the acceptability of the safety profile in relation to the expected benefit as well as if you consider the safety profile to be sufficiently characterised, in particular concerning CV safety

SAG agreed the principle that the safety of two co-administered drugs cannot be inferred from their individual safety profiles. The combination of fenfluramine and phentermine might be considered an instance of this.

In terms of pharmacology, topiramate acts on GABA receptors, on voltage gated ion channels, on aquaporins and inhibits of carbonic anhydrase. The psychiatric expert on the panel emphasised that he saw topiramate as an unpleasant medication of last resort for neuropsychiatric patients. Phentermine acts on adrenergic receptors in many organ systems.

Safety concerns derived from the use of the two agents individually are widely acknowledged; the case for their use in obesity therapy is entirely based around the principle that adverse effects are avoided or minimized at the low doses used in combination therapy. It is therefore essential to know the extent to which adverse events encountered at higher dose monotherapy have been eliminated by the new dosing schedule.

Specific concerns with regard to the safety profile were as following:

Neuropsychiatric Effects: The psychiatry expert pointed out that the safety profile was insufficiently characterized with regard to anxiety, given that the data were collected with screening instruments (such as the PHQ-9 score), and not a structured psychiatric assessment. His main concern was however with possible cognitive impairment, a known concern for the topiramate component, and also reported with Qsiva at the higher doses studied. This effect had not been captured sufficiently, and he advocated a further study to clarify the situation.

Depression was seen as less of an issue, but the expert was concerned about potential use of Qsiva with some classes of antidepressants. Given the increased rate of depression in obese people, and the limited familiarity of general clinicians with these agents, specialised guidance would be needed in this area.

Reported paresthesia with Qsiva therapy were also noted by SAG. These were reported in 17% of recipients of high-dose combination therapy, and were reported to be reversible in 75-80% of cases. This implies irreversibility in 3-4% of the treated population, and some SAG experts felt that further information should be supplied in this regard.

The cardiovascular safety profile based on the data presented in the Qsiva dossier did not give rise to immediate concern, apart from the observed increase in HR. It was appreciated that Qsiva appeared neutral or positive in terms of other proxy measures of cardiovascular risk. The cardiology experts agreed that no firm conclusion could be drawn one way or the other as to the safety implications of the relatively small increase in HR. While HR is recognized as a risk factor for future events in patients with cardiovascular disease, the small increase in HR might be relatively benign, or cancelled out by other favourable trends. Furthermore, the relevance of the increase in HR in this case is difficult to judge based on the available data, since this has not been fully characterized, e.g. with regard to median HR, variability of the HR, HR related to the time of medication etc. Pooled estimates might mask more pronounced patterns in a subset of patients.

Metabolic acidosis is associated with the use of Qsiva due to a known mechanism, was assessed during the procedure and is addressed in the proposed SmPC, and therefore was not part of the LoQ to the SAG. SAG did however feel that there were important unresolved issues to consider and therefore discussed the topic, since this side effect is prominent even at the lower dosage schedules used with Qsiva.

Nine cases of severe nephrolithiasis were reported in patients receiving high dose Qsiva. Topiramate, as noted, is a CA inhibitor, and is evidently effective in this respect even at the lower doses used in combination therapy. Thus, 16-30% users in the three treatment categories (vs. 5.9% placebo) had a bicarbonate below 21, and 1.7%, 1.6% and 2.0% (0.3% placebo) had reported values below 17. The Davenport curve implies that a bicarbonate of 21 is approximately equivalent to a pH of 7.35, and that a bicarbonate of 17 is consistent with a pH below 7.3.

The inability to excrete H^+ ions in the urine leads to metabolic acidosis and production of an alkaline urine that promotes the formation of calcium stones. Severe nephrolithiasis was reported in 0.6% of high dose users (NNH =180) in the course of relatively short term use in the clinical trials, but one might expect that risk to be progressive over time. Furthermore, metabolic acidosis also promotes calcium loss from bones, electrolyte disturbances and cardiac dysrhythmias. Dysrhythmias were seen in 4.7% on Qsiva vs. 1.8% for placebo. SAG has seen no arterial pH measurements, no measures of urine alkalinity, no measures of urine calcium and no measures of bone resorption. Respiratory acidosis is an added potential concern in those with respiratory failure associated with obesity, and osteoporosis would be a particular danger for overweight people.

Other safety-related concerns or information mentioned by individual experts during the meeting included the potential for increase in thromboembolic events in obese female patients due to the requirement of contraception; possible interaction between beta-blockers and phentermine, and the effect of discontinuation (rebound weight gain or psychiatric sequelae).

An additional concern expressed by some cardiologists is the possible interaction between Qsiva and other sympathomimetics as well as blockers of the sympathic system. Especially, the interaction with beta-blockers would be of concern due to the large use of these drugs in patients with CV-diseases and the possibility that Qsiva may reduce the beneficial effect of beta-blockers on CV-disease and therefore this interaction should be further studied.

In Summary: The unanimous view of SAG was that the dossier left a number of important questions unanswered, with the key areas as listed above: neuropsychiatric sequelae, cardiovascular parameters with regard to increase in heart rate, and the potential metabolic consequences. With no more than one or two exceptions, the 15 members of the panel supported the firm recommendation that each of these issues should be addressed as a precondition of marketing approval. This could potentially be achieved in the course of a relatively short (e.g. 6 month) additional study targeted to the issues that were raised. A properly designed and powered longer term cardiovascular risk study was also

considered to be essential, but not as a precondition of approval, and SAG was given to understand that such a study is already in the planning phase.

Although it is not within the remit of SAG to propose the design of studies to answer such questions, the following issues should be addressed:

Neuropsychiatric evaluation: The expert in this area believes that a proper assessment of the drug combination on cognitive function needs to be undertaken prior to approval. This would optimally be a dose response study in a small group of obese patients using an instrument such as CANTAB. In future studies of the product those patients who screen positive for depression or anxiety should have a proper structured psychiatric assessment, since a screening instrument does not produce a definite diagnosis. A comprehensive list of all psychotropic medications licensed in Europe and likely to interact with the product should be provided. For example in the US noradrenergic reuptake inhibitors such as lofepramine are not available but these are prescribed in Europe.

Cardiovascular evaluation: The cardiology experts recommended a specific study of e.g. 6 month duration, preapproval, to further characterize the HR increase associated with the mid dose use, measuring BP, pulse rate variability, and the detection of potential subsets within the data, using such tools as 24 hour ECG monitoring. This view was backed by the other experts present, although one of the cardiologists did not support the need of such data preapproval. If performed, such a study could also be used to address cognitive function measurements and thus answer both sets of questions.

Metabolic evaluation: Further data should be made available concerning metabolic consequences of treatment with Qsiva. These should include the degree of metabolic acidosis encountered at least at mid dose level, including direct measurements of pH, together with diurnal electrolyte balance, plasma and urine calcium concentrations, urine pH and bone density. Existing data held by the company may allow some of these questions to be addressed, but prospective analysis might be needed if some of these issues have not been fully addressed, and longer term surveillance studies should be undertaken post-approval.

2b) The safety issues would necessitate a careful identification of the appropriate patients as well as close monitoring. Please discuss the feasibility of adhering to such requirements in clinical practice.

SAG considered that there are still important unknowns about this agent. The concerns raised may well be dissipated by further knowledge and experience but, at the current state of knowledge, the strong view taken was that this agent should only be prescribed by specialised services or centres. This restriction was justified by the need for careful evaluation, monitoring and follow up, including detection of responders/non-responders based on clear treatment criteria. Moreover, the prescription by specialised services or centres is also essential to ensure the simultaneous integration into support services, including physical activity programmes, life style interventions and psychological support to achieve long-term behavioural changes. The psychiatric expert emphasized the need, already implemented to some extent in the SmPC, to screen carefully for psychiatric conditions such as severe mood disorders and to exclude those patients from treatment.

The definition of a specialised service or centre for the management of obesity gave rise to some debate, given the diversity of existing service provision within EU member states.

3. Please discuss the additional beneficial effect of the high dose versus the mid dose taking into account the clear dose dependent increase in most reported adverse events.

The difference in effect on weight reduction between high dose and mid dose was relatively small, and of the order of 1-2% after 2 years, whereas both differed markedly from placebo. The rate of adverse events did however show a disproportionate increase with the high dose, for which the benefit/risk ratio was therefore judged to be unfavourable. SAG took the unanimous view that the high dose should not be recommended for approval since the added benefit compared to the mid dose was relatively small and overshadowed by a disproportional increase in adverse events.

Final Comments: Since this report should reflect the distribution of opinion within SAG, it should be noted that at the end of the discussion, a small minority of the members were of the view that Qsiva should not go into clinical use at all. The remaining members placed greater emphasis upon the potential benefits of treatment for a group of patients currently denied any hope of effective therapy, and this viewpoint was appreciated by all. There was however near-unanimity concerning the need to address the 3 critical issues outlined above, likely necessitating further preapproval studies, and for cautiously phased introduction of this therapy.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Non-pharmacological treatment options (nutritional education, behaviour modification and increased activity and exercise) should always be first-line therapy for subjects with overweight/obesity. However, compliance to these treatment options is sometimes disappointing, and in such situations pharmacological treatment may be of value as an adjunct to dietary measures and physical exercise.

Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight, and thus these parameters are considered as relevant endpoints and surrogates for reduced CV risk (*guideline on clinical evaluation of medical products used in weight control, CPMP/EWP/281/96 Rev.1).*

In the current application, the Applicant presented the results from four phase 3 studies and five phase 2 studies to support the efficacy associated with the combination of phentermine and topiramate (PHEN/TPM). The duration of the studies were 28 and 56 weeks, while subjects included in study 305 which was an extension of one of the 1-year studies, were followed for a total of 108 weeks. Subjects with and without weight-related co-morbidities (defined as hypertension, increased TG, impaired fasting glucose or increased waist circumference) were studied.

The results of all studies supported a statistically and clinically relevant weight reducing effect of the 7.5/46 mg and the 15/92 mg dose. The mean body weight loss difference over placebo ranged from 7 kg for 7.5/46mg to 8-9 kg for the 15/92 mg dose. Qsiva 3.75/23mg appeared to be less effective with a mean body weight loss of 3.5 kg. In addition, data collected throughout the Qsiva clinical program, demonstrate that the response with the combination exceeds the response with either single agent.

Mean percentage weight loss from baseline was approximately 8 and 10 % for the 7.5/46 mg and 15/92 mg dose, respectively (1.2-1.8 % weight loss in placebo groups). Approximately, 62 and 67 % reached at least 5% weight loss, and 38 and 45 % reached 10% weight loss, with the two doses respectively (15-30 % and 7-11%, respectively in the placebo groups). As a historical comparison, the corresponding results in the main studies for previously approved products for weight control, rimonabant and orlistat, are given below:

	Approx. proportion of subjects with 5% weight loss after 1 year treatment	Approx. proportion of subjects with 10% weight loss after 1 year treatment
PHEN/TPM high dose	67 %	45 %
PHEN/TPM mid dose	62 %	38 %
Rimonabant	50 %	25 %
Orlistat	45 %	20 %

Weight reduction was similar and independent for gender, BMI, and co-morbidities. However, the difference in effect between the mid and high dose was somewhat more pronounced in subjects with high baseline BMI. For subjects with a BMI $\geq$35, the proportion of 10% responders was 37 and 47% for the mid and high dose, respectively.

There are no indications of a detrimental effect of PHEN/TPM on cardiovascular risk factors from the secondary efficacy parameters blood pressure, glucose and lipids, but rather a limited beneficial effect most likely secondary to weight loss since after weight stabilisation, no further improvement was observed.

Uncertainty in the knowledge about the beneficial effects

The claimed dose of QSIVA 11.25 mg/69mg was not evaluated in any of the pivotal studies. The dose should be used for up-titration only, but even if patients should remain on this dose, this would be acceptable considering that data is available for both higher and lower doses.

The number of subjects in Qsiva low-dose (n=240) and mid-dose groups (n=498) was significantly lower compared to the number of subjects in Qsiva full-dose group (n=1580) and placebo group (n=1561). However, the mid dose has shown a clinically relevant effect in all studies.

The experience in subjects older than 70 years and subjects with cardiac disorders is very limited.

The majority of the subjects had baseline BMI between 30 and 40 kg/m^2. The experience in subjects with BMI <30 kg kg/m^2 is limited, but there were no major differences in effect based on baseline BMI. The benefit of the treatment with respect to reduction of risk of CV events could be expected to be higher in subjects with severe obesity, e.g. with a BMI ≥35. The proposed indication includes patients with this cut-off and without co-morbidites. In patients with weight related co-morbidities, the proposed cut off is a BMI ≥30.

Long term data in the context of the aim to prevent cardiovascular events is limited. There is no withdrawal study available which is a deficiency when deciding on optimal duration of the treatment. Although, there was a mean weight gain in the second year of treatment, the treatment effect was largely preserved over 108 weeks in study 305. The available data do not indicate that body weight increases above baseline weight when withdrawing the treatment. In the cardiovascular outcome study the applicant is planning to undertake, changes in pre-selected endpoints (e.g., body weight, lipids, etc.) in patients who discontinue study drug during the trial are planned to be examined.

No results from outcome studies aiming to demonstrate direct, beneficial effect of weight reduction on the risk of cardiovasclular disease are currently available.

The pivotal phase 3 studies were exclusively performed in centres in the US. Life style, including eating habits but also the healthcare system, differs between the USA and the European Union. Some uncertainties may remain whether the results obtained in an American obese population would be similar in a European population.

Risks

Unfavourable effects

Known adverse events with the use of phentermine are palpitations, tachycardia, elevation of blood pressure, psychosis, CNS effects (insomnia, irritability, and headache), and GI effects (dry mouth, dysgeusia, constipation). Phentermine as amphetamine-like substance has a well known drug abuse potential. With topiramate monotherapy, paraesthesia, changes in taste, ocular disorders, psychiatric and cognitive disorders have been commonly reported. Topiramate is known as a teratogenic substance causing congenital malformations.

Many of these adverse events were also reported with the fixed-dose combination of PHEN/TPM, but there is no indication that any of these are aggravated compared to what is seen for the mono components. Further, the doses in the fixed-dose combination are considerably lower compared to the doses approved in the US for the single components.

The frequency of AEs increases with increasing dose, and is considerably higher in the maximum dose group. The difference between placebo, the PHEN/TPM 7.5/46 mg, and 15/92 mg group (in the 1-year cohort) is especially obvious for the nervous system disorders (placebo 9.5%, mid dose 24.5%, and high dose 34.5%), the gastrointestinal disorders (placebo 10.6%, mid dose 24.9%, and high dose 31.4%), and psychiatric disorders (placebo 6.3%, mid dose 9.8%, and high dose vs. 16.8%).

The SAE pattern reflects the AE pattern, with cases of depression (the incidences were higher in the PHEN/TPM 15/92 mg group than in the other treatment groups), anxiety (the incidences were higher in the PHEN/TPM groups than in the placebo group), decreased appetite, and anorexia noted. Overall, the PHEN/TPM 15/92 mg group had higher incidences of SAEs.

There was an increased incidence of depression with increasing dose (7.7% in the highest dose group, 3.8% in the mid dose group). The majority of the events of depression occurred within 90 days and resolved upon treatment discontinuation.

Approximately 28% of subjects in the Qsiva one-year cohort reported a history of any psychiatric disorder at baseline. The incidences of depression TME events were greater in those who had a history of depression as opposed to those who did not (11.4% versus 6.8% full dose). However, the relative risk of incident depression with Qsiva 15 mg/92 mg compared with placebo was 1.73 in subjects with a history of depression, and 2.72 in those with no such history. Therefore, a history of depression cannot be used to exclude subjects at higher relative risk of treatment-induced depression.

For anxiety, the highest incidence rate was found in the highest dose group (7.9%; for mid dose group 4.8%), and led to discontinuation for 25% of the subjects with anxiety reported. The relative risks of anxiety in the 1-Year cohort was 3.95 in subjects with history of anxiety and 2.76 in the rest of the population, although the absolute increases in risk were obviously different.

The incidence of insomnia was 6.7%, 6.8%, and 10.8% in low-, mid- and full-dose Qsiva groups compared to 5.7% in the placebo group.

Paraesthesia was a common adverse event in subjects exposed to PHEN/TPM. (Placebo: 1.2%, PHEN/TPM 7.5/46 mg: 11.8%, and PHEN/TPM 15/92 mg: 17.3%). The majority of the events were reversible.

Cognitive disorders (mainly attention disturbances, memory impairment and language disorders) were more frequent with PHEN/TPM treatment compared to placebo (1.5, 5.0 and 7.6% in the placebo, mid and high dose, respectively). The events most often occurred during initiation of treatment. The assessment of cognitive function was performed in one phase 3 trial of 6 months duration 6 months

with a not widely recognized RBANS scale. This was proposed by the applicant to be addressed further in studies which would have been performed post approval, including a specific study to assess cognitive disorders.

There were a higher proportion of subjects with cardiac disorders (mostly palpitations and increased heart rate) in the PHEN/TPM groups compared to placebo in the 1 year cohort (1.8% for placebo, 4.2% in the mid dose group, and 4.7% in the highest dose group). The mean change from baseline to Week 108 in heart rate was 0.4 bpm for the placebo group, 1.3 bpm for the PHEN/TPM 7.5/46 mg group, and 1.7 bpm for the PHEN/TPM 15/92 mg group. The proportions of subjects with an increase in heart rate > 10bpm from baseline at any time point during the studies were 42 % in the placebo group compared to 50.4% and 56.1% in the mid and high dose groups, respectively. Mean decreases in SBP and DBP were observed for all of the treatment groups. The mean decreases were larger for the PHEN/TPM groups than for the placebo group. The Applicant has analysed change in systolic blood pressure as a function of change in heart rate in the 1-Year cohort. The results showed that subjects with categorical increases in HR still demonstrated reductions in blood pressure compared to placebo.

A meta-analysis of CV events performed during the procedure indicated that a rather low CV risk population has been studied. Even though in the studied population there was no overall signal of an increased risk of CV events, the consequences of an increased heart rate in subjects with history of, or ongoing cardiovascular disease is unknown. This is planned to be evaluated in a CV outcome study, which the applicant is planning to perform, where an interim safety analysis is foreseen when 120 events have occurred.

Due to the inhibitory effect of topiramate on renal carbonic anhydrase, reductions in serum bicarbonate were recorded. Reduction < 21 mEq/L was seen in 2.1, 6.4 and 12.8% in the placebo, mid and high dose groups, respectively. Reduction < 17 mEq/L was seen in 0.1, 0.2 and 0.7% in the placebo, mid and high dose groups, respectively. There were 2 cases of metabolic acidosis (1 each in the mid and high dose groups). Renal stones were reported in 0.3 and 0.9% of patients in placebo and high dose groups, respectively. Body composition using DEXA in a subset of patients showed no change.

The teratogenic potential of topiramate was already known previously. Measures have been proposed by the Applicant to mitigate this issue including warnings in the SmPC and a medication guide to prescribers and patients.

Uncertainty in the knowledge about the unfavourable effects

There were few older subjects (defined as age ≥ 65 years) in the study programme (98 subjects in the placebo group, four subjects in the PHEN/TPM 3.75/23 mg group, 47 subjects in the PHEN/TPM 7.5/46 mg group, and 105 subjects in the PHEN/TPM 15/92 mg group), so no conclusions can be drawn from the safety evaluation for elderly. Information was proposed during the procedure to be added in the proposed SmPC, and the elderly identified to be'missing information' in the proposed RMP.

Cases of severe, often fatal, pulmonary artery hypertension (PPH) have been reported in subjects undergoing therapy with certain centrally acting anorectic agents. This has been seen with the serotonin releasing agents, but not with the serotonin re-uptake inhibitors. Furthermore, phentermine and fenfluramine have been prescribed concomitantly until 1997 as an appetite-suppressant and have been associated with varying degrees of valvular regurgitation and PPH when used together.

Phentermine use alone has not been associated with central or peripheral effects of serotonin, and no observation of such cases has been reported with the phentermine/topiramate fixed combination in the submitted clinical programme including a 6-month phase 2 study with echocardiogram investigation. Nevertheless, single cases of PPH and valvulopathies have been reported in literature when phentermine was used alone and warnings are included in the US product information. PPH and

valvulopathy therefore were proposed to be included as potential risks in the proposed RMP, and warnings to be included in the proposed SmPC.

Phentermine as amphetamine-like substance has a drug abuse risk. Tolerance to the anorectic effect may develop and an increase of dose could be required by subjects. There was no evidence for potential for drug abuse or withdrawal effects with Qsiva in the clinical development program and there was no evidence for the development of euphoria or dependence.

A description of the potential for misuse was proposed to be given in the SmPC. It has also been suggested by the applicant to evaluate the incidence of misuse via spontaneous ADR reporting, an EU Patient Registry, and, after a period of time in the market, via a Drug Utilisation Study.

The applicant has provided a presentation of the exposure in subjects with different functional levels of renal and hepatic impairment. In subjects with severe renal impairment, the recommendation not to exceed 3.75 mg would have been included in the proposed SmPC, due to the increased exposure and potential safety consequences.

Subjects with severe hepatic impairment have not been investigated and given the exposure increase in subjects with moderate hepatic impairment, it would have been now reflected in the proposed product information that treatment in severe hepatic impairment subjects should be avoided. There remain uncertainties regarding the interaction potential of phentermine and to some extent, the potential effect of other medicinal products on the exposure of phentermine.

Benefit-risk balance

Importance of favourable and unfavourable effects

Considering that several obese subjects do not respond to life style interventions as the only treatment and that obesity is considered as a risk factor for cardiovascular disease and associated with several other co-morbidities, the beneficial effects of Qsiva, with respect to weight reduction, being larger compared to previous and current alternatives are considered as being of high clinical importance. Loss of at least 5 to 10% in body weight is associated with beneficial effects on several CV risk factors and is considered as a surrogate for reduced CV risk. However, this would imply a weight loss maintained long term and an associated decrease of CV risks factors, both of which are uncertain. Nevertheless, no results from outcome studies showing a direct, beneficial effect of weight reduction on the CV risk are currently available. Such studies would require long duration and have so far not been requested to support approval of a weight control product. Patients with high BMI have very few additional treatment alternatives and are also expected to receive other beneficial effects on orthopaedic conditions, sleep apnoea etc. Qsiva is proposed to be recommended for obese patients with BMI $\geq$ 35 kg/m^2 or for obese patients with BMI $\geq$ 30 kg/m^2 and with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia, i.e. a population with a high medical need.

Available data show that the effect of the recommended dose, 7.5 mg/46 mg, is largely maintained over 2 years of treatment. However, e.g. blood pressure was reduced after 1 year but no longer significantly so at 2 years versus placebo. This dose has not been extensively studied (with 349 patients exposed for one year and among them only 153 patients treated for 2 years). There is no withdrawal study available and therefore information on subsequent weight gain, changes in CV risk factors and CV event rates were missing, which was considered a deficiency in particular when deciding on optimal duration of the treatment. However, it can be assumed that, as for other drugs, the effect will vanish once treatment is discontinued.

Concerning safety, it is noted that topiramate is already approved in the EU in doses of 200 and 400 mg for migraine prophylaxis and treatment of epilepsy, respectively. Phentermine has been approved in the US in a 37.5 mg dose since 1959 without concerns regarding serious CV events.

However, a number of adverse events have been identified with uncertainties with regard not only to CV safety related to increase in heart rate but also in the key areas of neuropsychiatric sequelae and metabolic consequences long-term.

The most common adverse events in the clinical studies were gastrointestinal and neurological (in particular paraesthesia) with a higher incidence in subjects receiving the high compared to the low dose. These events were in general reversible, and it could be expected that such events would most likely result in discontinuation of treatment and may thus not be a serious concern.

The increased incidence of psychiatric disorders, in particular depression and anxiety, in particular with the high dose, raises concerns about the possibility of a safe use of Qsiva in clinical practice in which the absolute risk may be higher compared to the clinical trial setting. No patient group with a lower risk has been identified.

Cardiovascular safety of drugs intended for long term treatment of patient groups at increased risk of CV events (e.g. subjects with type 2 diabetes, hypertension, hyperlipidaemia, obesity) is of great importance. One of the aims of these treatments is to reduce the risk of CV events, and consequently, an increase of such events would not be acceptable. Phentermine increases heart rate due to its mechanism of action. However, the increase in HR is limited and is not associated with increase in blood pressure but rather a reduction. However, the impact of an increase in HR in patients with CV disease and/or early stages of heart failure is not known.

Phentermine in combination with fenfluramine has been associated with valvular regurgitation and PPH. Since phentermine has not been associated with central or peripheral effects on serotonin (which is considered as the mechanism behind these adverse events), and no observation of cases of valvular regurgitation and PPH has been reported with the phentermine/topiramate fixed combination in the clinical studies,.

Considering the known teratogenic potential of topiramate in the context of the target population, largely consisting of women with child-bearing potential, measures to avoid pregnancy were considered to be of outmost importance. This has been addressed in the proposed RMP which includes a prescribers' and subjects' medication guide, the proposed SmPC which reflects the teratogenic potential of TPM and by the proposal to restrict prescription to 30 days' supply.

Most of the reported adverse events were dose dependent. The highest dose is proposed to be reserved for patients with a BMI ≥35 despite 6 months treatment with the mid dose and who tolerate this dose well. Further, only patients who have achieved a ≥5% weight reduction after 12 weeks treatment should continue treatment with Qsiva.

Considering that treatment will have to be continued long term and a wide spread use could be expected, it is important that safety can be monitored in a relevant manner in clinical practice. Proposals with that regard have been made but compliance with the SmPC provisions and the feasibility of monitoring the risks in the clinical setting have been questioned.

Benefit-risk balance

The benefit/risk balance of Qsiva is considered as negative.

Discussion on the benefit-risk balance

The weight-lowering effect of Qsiva is of clinical relevance and could potentially translate into benefits for orthopaedic conditions and sleep apnoea, as well as psycho-social and cardiovascular benefits. However, there are concerns about the long term cardiovascular safety, adverse psychiatric effects, adverse cognitive effects, and potential metabolic and teratogenic risks. Such concerns, and the magnitude of the uncertainty about them, at the present time outweigh the demonstrated benefits.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Qsiva, in the treatment of

Obesity, including weight loss and maintenance of weight loss in adults, as an adjunct to reduced calorie diet and physical activity. Qsiva is recommended for obese patients (BMI ≥ 35 kg/m^2), or obese patients (BMI ≥ 30 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia. Qsiva should be prescribed by physicians experienced in the management of obesity and obesity-related co-morbidities.

the CHMP on 18 October 2012 considered by majority decision that the safety of the above mentioned medicinal product was not sufficiently demonstrated, and, therefore recommended the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considered that:

1. The long term cardiovascular safety of Qsiva has not been sufficiently established. Phentermine's mechanism of action is of concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. It is only being approved for short term periods of treatment (less than three months) and its long term cardiac toxicity is unknown. The currently available cardiovascular outcome data for Qsiva is considered inconclusive.

2. The frequency of adverse psychiatric effects and their consequences, in particular resulting from the topiramate component, is unknown in the setting of long term use of this product in a large population. In addition, the cognitive effects of such combination during long term treatment have not been sufficiently addressed.

3. Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard to the teratogenic risk of the product when used in a less controlled real life setting.

4. The probability of off label use of this product outside the suggested population is expected to be high. The risk minimisation measures as proposed by the applicant to limit such off label use were considered difficult to set up in practice.

For these reasons, the benefit/risk of Qsiva in the proposed indication of weight reduction in very obese patients or patients with obesity and weight-related co-morbidities was considered as negative.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and post authorisation measures to address other concerns as outlined in the list of outstanding issues could not be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, was of the opinion that it is not appropriate to conclude on the new active substance status at that time.

Re-examination of the CHMP opinion of 18 October 2012

Following the CHMP conclusion that Qsiva was not approvable for the treatment of

Obesity, including weight loss and maintenance of weight loss in adults, as an adjunct to reduced calorie diet and physical activity. Qsiva is recommended for obese patients (BMI ≥ 35 kg/m^2), or obese patients (BMI ≥ 30 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia. Qsiva should be prescribed by physicians experienced in the management of obesity and obesity-related co-morbidities.

because the safety of the above mentioned medicinal product was not sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) Diabetes Endocrinology with additional experts, inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response. The applicant provided with the grounds for re-examination revised Summary of Product Characteristics (SmPC) and risk management plan (RMP) proposals. The proposed RMP was assessed at the request of the CHMP by the Pharmacovigilance Risk Assessment Committee (PRAC). The applicant presented in writing and at an oral explanation their grounds that the adopted CHMP Opinion may not have considered the data fully and also provided further analyses to support the clinical safety of Qsiva in the proposed indication.

The applicant presented in their submission the following grounds for re-examination:

The applicant emphasises that Qsiva is highly effective in achieving and maintaining weight loss in obese patients, of a magnitude greater than that of any other pharmacological treatment to date with expected improvement of cardiovascular, metabolic, and other outcomes, as well as demonstrated improvements in blood pressure, glycaemic control, lipids, quality of life, incidence of new onset type 2 diabetes and other outcomes. With regard to the general safety profile, the applicant points out that Qsiva is a combination of two approved drugs with long histories of use at higher doses and well established safety profiles of both components.

The applicant addresses specifically the CHMP´s four initial principal grounds for refusal:

Ground 1

The long term cardiovascular safety of Qsiva has not been sufficiently established. Phentermine's mechanism of action is of concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. It is only being approved for short term periods of treatment (less than three months) and its long term cardiac toxicity is unknown. The currently available cardiovascular outcome data for Qsiva is considered inconclusive.

Grounds for re-examination, applicant's position:

<u>Sympathomimetic properties of phentermine</u>

Consistent with the submitted evidence, the Applicant points out that any change in heart rate is dose-related, that there is no increase in heart rate at the mid-dose relative to placebo, and that significant reductions in blood pressure are preserved at all doses, even in the face of a small increase in heart rate on the top-dose. The Applicant has also provided objective, scientific evidence regarding cardiovascular safety actually observed during two years of experience with Qsiva in thousands of

patients in randomised, well-controlled clinical trials. Consistent with the prevailing Rules, Regulations and Guidance regarding applications for marketing authorisation of a weight loss product, there is no requirement for the applicant to establish "long term cardiovascular safety" prior to approval in the EU for the purpose of evaluating benefit/risk balance underlying the grant of a marketing authorisation. No safety signal of cardiovascular risk was identified in the clinical development program, and the point estimates of cardiovascular risk using six different composite cardiovascular outcome endpoints were all less than 1.0.

It is important to recognise the fact that Qsiva is NOT synonymous with phentermine. Qsiva is a combination of low dose phentermine with low dose topiramate. Therefore, cautions should be exercised in extrapolating safety from medicinal product containing high dose phentermine to low dose phentermine as contained in Qsiva to ensure fairness in the safety assessment of Qsiva. Neither low dose phentermine nor Qsiva should be classified as a typical cardiac-stimulating sympathomimetic without consideration of dose response or, most importantly, the overall cardiovascular pharmacodynamic profile as evidenced by the objective clinical and cardiovascular safety observed during two years of experience with Qsiva. There was no significant increase in heart rate at the mid-dose, the recommended dose expected to be used by most patients.

The safety dataset submitted by the Applicant includes an assessment of cardiovascular safety and outcomes, for treatment with Qsiva for up to two years, and the assessment showed no cardiovascular safety signal of concern. The totality of the safety data set in the Applicant's MAA has met or exceeded the current requirements for weight loss drugs and the accepted international regulatory requirements and standards in ICH E1A Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95).

Approval of Phentermine for short term use

The historical origins of the 3-month limitation on the duration of treatment with phentermine as a single agent include a) the observations of tolerance developing within the first three months of treatment, b) concern regarding potential abuse liability, c) the limited or non-existent longer-term data available at the time of approval 53 years ago, based on the regulatory requirements in effect at the time and d) the lack of any incentive to support long-term clinical trials of a generic, non-proprietary drug. The 3-month limitation was not imposed in response to any safety signal. The limitation has not been lifted simply because no entity has been willing to fund and conduct the required clinical trials for a generic, non-proprietary drug. In "everyday medical practice", US physicians who treat large numbers of patients for obesity routinely use phentermine on a chronic basis, well exceeding the labelled treatment duration of three months. The Applicant also collected and submitted data from a clinical trial (OB-301) in which phentermine alone was administered for six months with no significant safety or tolerance issues, and no evidence of abuse liability.

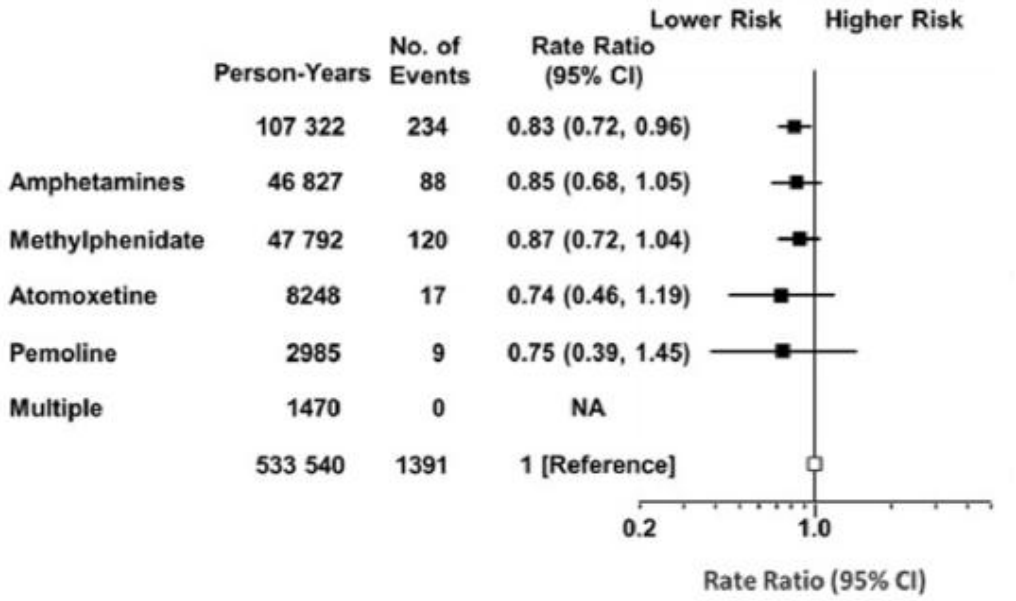
With regard to Qsiva per se, a) there is no evidence of tolerance, b) there is no signal or evidence of abuse liability of the combination product, c) the Applicant has provided longer-term data on treatment up to two years that do not indicate any increase in cardiovascular risk and d) the Applicant has committed to conduct a large, event-driven, international, long-term cardiovascular outcomes trial within a timeframe defined by the US FDA, to further characterise long-term cardiovascular safety. This approach is entirely consistent with the newly adopted EU pharmacovigilance legislation to proactively collect information relevant to ongoing evaluation of benefit/risk balance of a marketed product.

The literature regarding the longer-term use of phentermine is limited, but one recent paper reported experience with phentermine treatment for periods up to eight years, at doses as high as 93 mg per day. In this study, no increase in cardiovascular risk was observed, and both heart rate and blood

pressure were actually reduced, as measured by automated instruments averaging multiple measurements at each visit.

Although there are little data on long-term cardiovascular outcomes of phentermine exposure, per se, there are now scientifically compelling data available regarding the cardiovascular safety of the stimulants amphetamine and methylphenidate in the treatment of young and middle-aged adults with attention-deficit/hyperactivity disorder (ADHD). Treatment with these drugs has been shown to increase both heart rate and blood pressure. This paper reported the results of a retrospective, population-based cohort study based on the electronic medical records of 443,198 subjects representing 806,182 person-years of follow-up. Each medication user (n=150,359) was matched to two non-user controls. Cardiovascular endpoints included myocardial infarction (MI), stroke, and sudden cardiac death (SCD). The adjusted rate-ratio (RR) of serious cardiovascular events for use versus non-use of ADHD medications was 0.83 (95% CI, 0.72-0.96). Results were similar in both young and middle-aged adults, and in subjects with or without a history of cardiovascular disease. The forest plot depicted as Figure 7 **Error! Reference source not found.**shows the RR of all drugs combined and for each individually. Even the RR of amphetamine when analysed individually was 0.85 (95% CI 0.68-1.05).

Figure 6. Cardiovascular Risk Associated with Stimulant Medications



The use of ADHD medications, including amphetamine and methyphenidate, is not associated with an increased risk of serious cardiovascular events. Although these data do not entirely substitute for the cardiovascular safety of phentermine specifically, they do provide reassurance regarding amphetamine, a drug which is known to elevate both heart rate and blood pressure, and to which phentermine is often compared.

Since heart rate remains a concern of the Committee, it seems relevant to examine the effect of other drugs, used in similar population, which increase heart rate on cardiovascular risk. For example, the cardiovascular effects of the GLP-1 agonists exenatide and liraglutide have been investigated, including their effects on blood pressure, heart rate, and the cardiovascular outcomes of arrhythmias, heart failure, nonfatal myocardial infarction, stroke, and death. Both GLP-1 agonists reduced systolic blood pressure by 3-5 mmHg, but increased heart rate by 2-4 bpm. In a meta-analysis of 15 Phase II and III studies, cardiovascular outcomes were assessed in 6638 patients, with 4257 exposed to liraglutide. In this analysis, the outcomes of MACE events (in this case, non-fatal MI, stroke, and death) favored

liraglutide, with an incidence ratio of 0.73, and the upper bound of the 95% CI of 1.41. Similar results were obtained from cardiovascular outcomes studies of exenatide, with a hazard ratio for MACE events of 0.7, favoring exenatide. Despite the increase in heart rate of 2-4 bpm with both exenatide and liraglutide (more than double the increase observed with the top-dose of Qsiva), the risk of major adverse cardiovascular events was not increased. On the contrary, cardiovascular outcomes favored both GLP-1 agonists. It is also important to note that agents which selectively reduce HR (e.g., ivabradine) did not show the expected improvement in hard CV endpoints despite a significant reduction in mean HR, thus further weakening the association between small changes in HR and CV risk.

Long term cardiac toxicity

Despite a 53-year history of use, phentermine, under normal conditions of use, has never been causally linked to myocardial infarction, stroke, congestive heart failure, valvular heart disease, pulmonary hypertension, or death. During this time, phentermine has been used in millions of patients, at higher doses, for at least 8 years of continuous use.

Inconclusive cardiovascular outcome data for Qsiva

Long-term cardiovascular outcome data are not required by the prevailing Rules, Regulation or Guidance for approval of new weight loss products in the EU. However, the Applicant believes the clinical trial data submitted to be conclusive for use in our study population over a two year treatment period, which is consistent with, and well-supported by the 53 year history of phentermine use, and the 16 year history of topiramate use. The Qsiva clinical development program was not designed or intended to be a cardiovascular outcomes trial, but rather to satisfy the regulatory requirements in effect for a weight loss drug at the time of the trials and the submission of the Application. Nonetheless, more than 4500 subjects were studied, some for as long as two years, offering some insights into the cardiovascular safety of the drug. Cardiovascular safety was assessed by comparisons of cardiovascular event frequencies and severity. Comparisons of Major Adverse Cardiovascular Events (MACE) were made using six different composite endpoint definitions, including those cited by the US FDA for cardiovascular outcomes trials. Definitions for each of these endpoints are as follows:

a. Cardiovascular Death, MI, and Stroke;

b. JUPITER trial major adverse cardiovascular events (MACE): Cardiovascular Death, MI, Stroke, Coronary Revascularisation, and Unstable Angina;

c. FDA MACE: Cardiovascular Death, MI, Stroke, Coronary Revascularization, Unstable Angina, and Congestive Heart Failure;

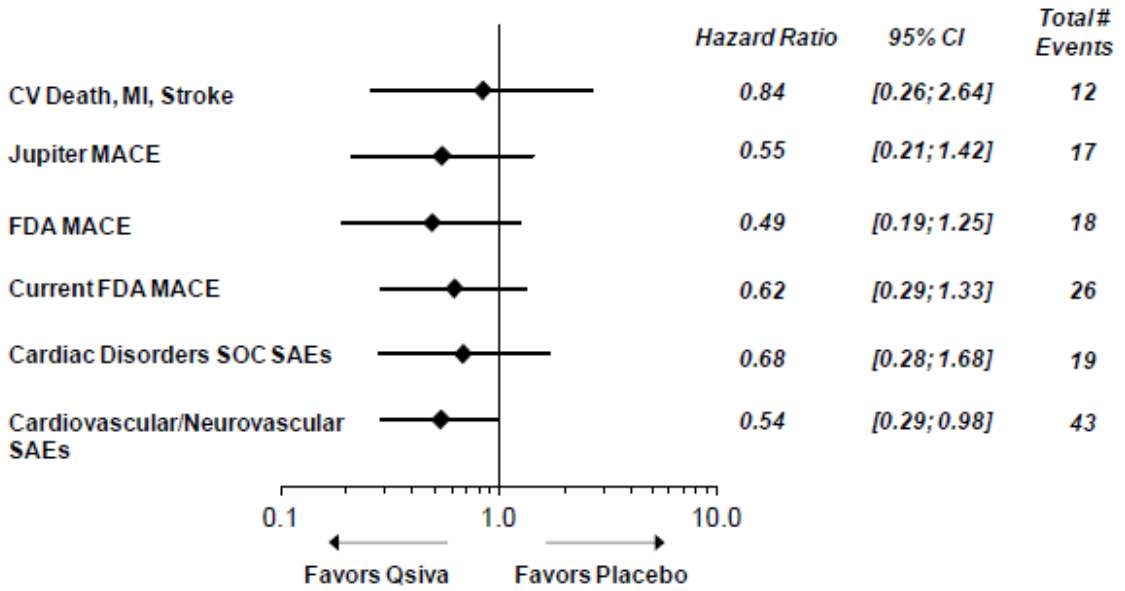
d. Revised FDA MACE: Cardiovascular Death, Acute Coronary Syndrome (Nonfatal MI and Unstable Angina), Cerebrovascular Events (Non-fatal Stroke and Transient Ischemic Attack), Coronary Revascularization, Hospitalization for Heart Failure, Stent Thrombosis, Hospitalization for Other Cardiovascular Causes, Carotid Artery Revascularization, Peripheral Vascular Revascularization, Lower Extremity Amputation, Hospitalization for Cardiac Arrhythmia;

e. Cardiac Disorders System Organ Class (SOC) SAEs: All SAE preferred terms mapping to the Medical Dictionary for Regulatory Activities (MedDRA) Cardiac Disorders SOC;

f. Cardiovascular and Neurovascular SAEs: All SAE preferred terms mapping to the MedDRA Cardiac Disorders SOC, and SAEs with preferred terms of deep vein thrombosis, hypertension, hypotension, brain stem infarction, cerebral infarction, cerebrovascular accident, haemorrhage intracranial, transient ischemic attack, chest pain, non-cardiac chest pain, and pulmonary embolism.

As shown in Figure 7, the point estimates of risk were less than 1.0 for all six composite endpoints, and the upper bounds of the 95% confidence intervals were less than 1.8 for all but the most restrictive, triplicate endpoint. The confidence intervals for the triplicate endpoint were larger because of the smaller number of events and therefore least statistical precision.

Figure 7. Hazard Ratios for Qsiva vs. Placebo for Multiple Composite Endpoint Definitions of Major Cardiovascular Events – All Exposed Subjects



Although based on a small number of events, it is reassuring to note that the point estimates for all six composite endpoints were less than 1.0. Cardiovascular outcomes and surrogates of risk were also compared in multiple subpopulations. None of those analyses was able to identify a subpopulation which incurred a greater risk of serious cardiovascular events on active treatment. The Applicant recognises that a history of commercial use with incomplete and potentially biased reporting of adverse events does not represent the same quality of data as that provided by randomised and well-controlled clinical trials. However, the 53 (phentermine) or 16 years (topiramate) of widespread commercial use in millions of patients at much higher doses represents more experience in everyday clinical practice with phentermine and topiramate than any clinical trial could possibly provide. The Applicant believes that if no signal of significant cardiovascular risk has been identified by pharmacovigilance within the existing collective history, it is unlikely that any clinical trial of realistic size and duration could do so. If, as expected, any increase in cardiovascular risk is smaller than the differences typically assessed in published outcomes trials, the sample size required to "conclusively" and precisely quantify that difference would be prohibitively large.

There is no evidence from the 53-year commercial experience with phentermine or from the well-controlled Qsiva clinical trials up to two years in duration that this drug alone or in combination with topiramate, in the doses used in Qsiva, measurably increases cardiovascular risk in the population for which Qsiva is intended. Nonetheless, the Applicant will be conducting a large, event-driven, cardiovascular outcomes trial, and will include appropriate precautions related to cardiovascular risk in the RMP.

In the one-year cohort, heart rate was increased by 1.6 bpm on the top-dose of Qsiva, but the change in heart rate on the mid-dose was indistinguishable from placebo. The small increase in heart rate on top-dose was substantially less than the intra-subject variability of the measurement. The standard deviation of heart rate in this cohort was approximately 10 bpm. Blood pressure and rate-pressure

product were consistently reduced on active treatment, including subjects with significant elevations in heart rate.

Data provided in the submission demonstrate that most of the small observed increase in mean heart rate occurred in subjects within the lowest tercile of baseline heart rate (<60 bpm) at study entry, that heart rate was essentially unchanged in subjects within the middle tercile (60-90 bpm), and that heart rate was generally reduced in subjects within the highest tercile (>90 bpm), arguably at greatest risk, at study entry. Collectively, these observations suggest a regression to the mean in heart rate during the study.

In the one-year safety cohort, 12.8% of all subjects were receiving a beta-blocker at baseline. Within this subpopulation, comparison of placebo subjects to those on active drug demonstrated that Qsiva did not abrogate the effect of beta-blockers on blood pressure or heart rate.

Using the Framingham criteria, subjects treated with Qsiva showed dose-related reductions in 10-year risk assessment scores. Reductions for both the mid- and full-dose of Qsiva were significantly greater than those associated with placebo.

Unlike the Framingham and most other algorithms used for assessment of cardiovascular risk, the Cooper Clinic Mortality Risk Score incorporates heart rate (a dichotomous classification of ≥80 or <80 bpm) as well as age, blood pressure, diabetic and smoking status, BMI, and cardiovascular fitness into its calculation. Subjects treated with Qsiva showed a dose-related improvement in 10-year mortality risk as calculated by the Cooper Clinic method, and the comparison of the full-dose of Qsiva to placebo was significant.

Thus, using these validated predictive tools, the overall cardiovascular effect of Qsiva in obese subjects would be predicted to be favourable, with the declines in blood pressure, improved metabolic parameters (including lipids and measures of insulin sensitivity), favourable changes in inflammatory markers (reduction in CRP and increase in adiponectin) likely outweighing any potential increase in risk attributable to the very small increase in heart rate on top-dose, and certainly on mid-dose, in which there was no significant change in heart rate relative to placebo.

The Applicant recommends as part of the proposed conditions of use to be included in the SPC that heart rate and blood pressure are measured and recorded at every visit, in every patient treated with Qsiva. As a further risk minimisation measure, the Applicant has added instructions to the SPC and the prescriber checklist to require regular monitoring of HR and recommends dose reduction or discontinuation of treatment with Qsiva altogether in any patient whose heart rate increases from baseline by 20 bpm or is ≥90 bpm on two consecutive measurements.

In routine clinical practice, increases in resting heart rate are usually associated with a concurrent increase in blood pressure, and it is difficult to isolate the effect of each parameter on risk. Significant elevations in heart rate have been reported to increase cardiovascular risk, particularly at high absolute rates, but less frequently when outcomes data were corrected for the effects of blood pressure in the same patients, often on a background of established cardiovascular disease, and only when comparisons are based on fractiles or absolute numerical increases in heart rate which are substantially larger than the 1.6 bpm increase observed on the top-dose of Qsiva. It appears that the change in risk is not linear, but increases more rapidly for each fractile at higher absolute rates. Thus, a significant difference in risk can be identified within the highest fractile of heart rate (e.g., >90 bpm) compared to the lowest fractile (e.g., 58-73 bpm) in the same cohort, but, to the Applicant's knowledge, never between smaller increments of heart rate, such as 1-2 bpm. Some authors have suggested a minimum absolute threshold of 80-90 bpm for a significant increase in risk.

It is critical to consider that the vast majority of studies reporting an increase in cardiovascular risk with increased heart rate are retrospective and observational in nature. Thus, it is unknown whether

the association represents cause and effect, or if instead, the observed increase in heart rate is simply a marker which accompanies an underlying pathologic process. The Applicant is not aware of a single peer-reviewed publication of a prospective, interventional study, in the sense that a control group would be given a placebo and the active group given a drug with the specific intent to increase heart rate by a specified percent, absolute numerical bpm delta, or reach a certain absolute threshold of bpm. Predefined outcomes endpoint(s) would be compared over a specified duration of treatment. The most directly relevant data on this issue derive from large meta-analyses of cardiovascular outcomes in patients treated with an anti-diabetic drug known to increase heart rate. Both of the GLP-1 receptor agonists exenatide and liraglutide reduce systolic blood pressure, but increase heart rate by 2-4 bpm. Despite the increase in heart rate (more than twice that observed with Qsiva at the top-dose) cardiovascular outcomes actually favoured the GLP-1 agonists (Hazard Ratio ≈ 0.7). Conversely, as outlined earlier, a prospective trial of a pure heart rate-lowering drug, ivabradine, failed to show an improvement in outcomes despite a 6 bpm reduction in heart rate.

There are no data and no methods currently available to quantify any detectable increase in cardiovascular risk attributable to an increase in heart rate of <2 bpm on the top-dose (but not the mid-dose) of Qsiva, occurring within an absolute numerical range of 70-72 bpm, as observed in the pivotal trials of Qsiva.

In contrast, there are excellent data linking changes in blood pressure to cardiovascular risk. Each 2 mmHg reduction in systolic blood pressure confers a 7% reduction in cardiovascular mortality and a 10% reduction in stroke mortality. Blood pressure reductions on Qsiva were substantially greater than the 2 mmHg conferring the reported reduction in risk. It is equally clear that untreated obesity imparts a large increase in premature mortality and cardiovascular risk. Weight loss approximating 10% or more of body weight reduces these and other risks. Weight loss of this magnitude or greater was achieved in the Qsiva pivotal trials.

As indicated in the submission and the study protocol, the Qsiva pivotal trials did not select only "healthy" subjects and accordingly the results can be properly extrapolated to the target population for which Qsiva is intended. The study population of obese subjects is, by definition, already at increased cardiovascular risk. The only relevant exclusions according to the study protocol were for subjects with a recent myocardial infarction, or stroke, higher NYHA classes of heart failure, potentially life-threatening arrhythmia, or other established cardiovascular disease. Rarely were patients excluded by these criteria from study participation. The Applicant proposes to contraindicate the use of Qsiva in these higher-risk patients in the SPC and incorporate this in the RMP, including the prescriber checklist until long-term outcomes data in such patients are available.

There may still be a potential concern within the CHMP of a possible association of phentermine exposure with a potential risk of valvular heart disease (VHD) and/or pulmonary hypertension (PH or PAH). The Applicant makes reference to the large body of available epidemiologic and mechanistic evidence which convincingly supports the conclusion that phentermine is not linked to these disorders. Since fenfluramines were withdrawn from the US market in 1997, only two individual case reports worldwide have suggested and association phentermine monotherapy and VHD or PAH. Based on the data available, the Applicant considers these cases to be confounded in terms of causality assessment; both the Applicant and the CHMP has had access to these two case reports to inform an independent and objective safety assessment. Despite a coincidental temporal association with phentermine exposure, the VHD and PAH in these two cases resulted from a mechanism other than exposure to phentermine. They provide insufficient signal of causation by phentermine monotherapy according to the accepted methodological approach to causality assessment.

In summary, the increase in heart rate of (+1.6 bpm) was associated with the top dose of Qsiva, but there was no significant increase in heart rate on the mid-dose. Unlike sympathomimetics, however,

both doses of Qsiva were associated with significant and clinically relevant reductions in blood pressure (-5.2 mmHg). Assessment of CV outcomes using various accepted MACE composite endpoints in the Qsiva development program showed no increase in risk for any of these endpoints compared to placebo (all hazard ratios less than 1.0). These results are consistent with the largest epidemiology cohort study conducted recently on sympathomimetics, which also showed no increase in MACE in ADHD patients with and without CVD. The components in Qsiva are not new chemical entities but rather low doses of topiramate and phentermine, both of which have been used safely by millions of patients at higher doses over many, many years. The US FDA continues to approve new formulations of phentermine, and its use has been steadily increasing over the past 10 years with millions of prescriptions used annually. On the totality of the data submitted in the applicant's MAA, the safety of Qsiva has been sufficiently established in accordance with the current requirements for the development of weight loss drugs and the accepted international regulatory requirements and ICH standards. While the theoretical long-term risk of 1.6 bpm increase in heart rate accompanied by a concurrent decrease of 5.2 mmHg in blood pressure cannot be definitively excluded at this time, it can certainly be managed by inclusion of appropriate wording in the SPC and implementation of an agreed RMP.

Ground 2

The frequency of adverse psychiatric effects and their consequences, in particular resulting from the topiramate component, is unknown in the setting of long term use of this product in a large population. In addition, the cognitive effects of such combination during long term treatment have not been sufficiently addressed.

Grounds for re-examination, applicant's position:

The frequency of adverse psychiatric effects and their consequences, in particular resulting from the topiramate component, as well as cognitive effects, are in fact well-known in the EU and elsewhere, based on more than 16 years of use of topiramate for migraine prophylaxis and epilepsy in Europe and the US. The potential for psychiatric and cognitive effects is widely recognised and has proven to be manageable with appropriate labelling and other measures during this time. Topiramate continues to be widely prescribed in the EU, without restriction, and without any requirement for a RMP.

With respect to the Qsiva clinical study program, the Applicant has provided up to two years of data in a relevant patient population that included a substantial percentage of patients with a history of depression and those using antidepressants at baseline. The duration of safety data provided by the Applicant exceeds the requirements described in guidelines for obesity products, and was deemed acceptable by the SAWP during discussions for this product specifically. The program also included prospective assessments of depression status (PHQ-9) and suicidality (C-SSRS) in all patients at all study visits, thereby providing assurance that if any untoward psychiatric signals were present for Qsiva, they would not go undetected. Based on data submitted within the Qsiva application, conclusions regarding psychiatric effects can be summarised as follows.

Although there was an increase in reports of psychiatric symptoms with the top dose of Qsiva that is consistent with the known CNS effects of topiramate, the majority of these events were of mild severity, occurred early in treatment, resolved spontaneously or with discontinuation of study drug, and did not result in significant medical sequelae. There were no such increases relative to placebo on the mid-dose. Indeed, it is important to note that the incidence of depression (2.2% vs. 2.8%), anxiety (1.9% vs. 1.8%) and insomnia (4.7% vs. 5.8) were similar between placebo and the mid dose, respectively.

Most reports of symptoms associated with or coded by MedDRA to "depression" did not actually represent major depression syndromes or mood disorders as defined by DSM-IV-TR criteria. In contrast to symptom reports, there were no dose-related increases in episodes of major depression as indicated by PHQ-9 responses or DSM-IV criteria, episodes that resulted in new antidepressant treatment or other medical intervention, or suicidal ideation with the intention to act or suicidal behaviour as captured by the Columbia Suicide Severity Rating Scale as shown in Table 9.

Table 9. Rates of Major Depression, Emergent Antidepressant Treatment, Serious Depression and Suicidality in the 1-year Study Cohort

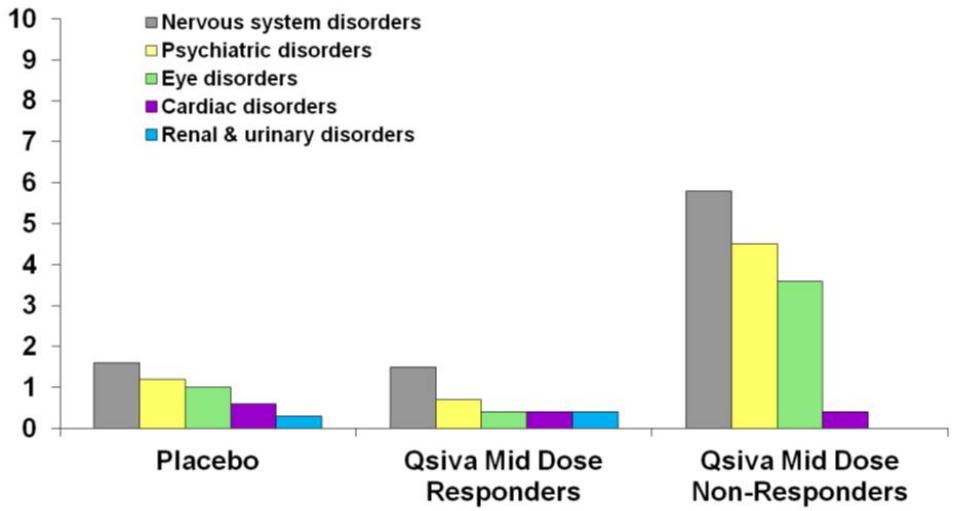
Subjects, %	Placebo N=1561	QSIVA Low N=240	QSIVA Mid N=498	QSIVA Top N=1580
PHQ-9 Major Depression*	2.8	3.3	1.6	3.1
Emergent Antidepressant treatment	3.7	4.6	2.4	3.0
Serious Depression	0	0	0	0
Suicidality	0.7	0.4	0.6	0.9

In the 1-year cohort there were no episodes of serious depression. Across the entire program, only one study patient (a placebo patient during year 2) experienced a serious depression episode. It should also be noted that suicidality, as reported in 2, consisted entirely of suicidal ideation without intent to act. There were no instances of ideation with intent to act or suicidal behaviour during the clinical trial program.

Across all dose levels, rates of depressive symptoms and major depression diagnoses were lower during year 2 than year 1, providing reassurance that events were not missed due to an insufficient duration of follow-up.

Furthermore, one of the stopping rules recommended by the Applicant in the SPC specifies that non-responders (defined as those who do not lose at least 5% of body weight within the first three months of treatment) should be discontinued from Qsiva after three months. Figure 8 shows that early discontinuation of mid-dose non-responders according to this rule eliminates the majority of subjects who would otherwise discontinue later for an adverse event. The mid-dose responders who remain are indistinguishable from placebo in the rate of later discontinuation for an adverse event. A similar relationship is observed on the top-dose.

Figure 8. AEs leading to discontinuation by SOC [%]



In addition to the measures previously proposed to manage potential risks associated with depression, the Applicant is prepared to work with the Committee on the most appropriate wording to be included in the SPC to optimise the safe and effective conditions of use of Qsiva, particularly as it pertains to sections 4.1-4.4 including, but not limited to, the intended population or approved doses. The SPC describes in details appropriate patients with respect to psychiatric conditions and their management. The RMP will ensure that prescribers are well informed about these issues and the prescriber checklist will ensure regular targeted follow up.

Although not expressly indicated by the CHMP as one of the Grounds for Refusal, for the sake of completeness in the overall safety assessment, the Applicant also evaluated any longitudinal changes in cognitive function with validated instruments in four different clinical trials. Small changes in attention/working memory appeared within the first four weeks of treatment, did not progress, rarely led to discontinuation, and were completely reversible within one week of discontinuing treatment.

In summary, the dose-related psychiatric effects of Qsiva are consistent with the known dose-related CNS effects of topiramate. The Applicant prospectively employed various psychometric tools to further characterize these effects in the Qsiva development program that studied a relevant population of obese subjects with and without psychiatric history or concurrent use of psychotropic medications. There was no increase in major depressive disorder, new uses of psychiatric medications, PHQ-9 scores, or C-SSRS measures of suicidality on either the mid-dose or the top-dose relative to placebo. There was nothing new or unexpected. Although there was an increase in reports of psychiatric symptoms with the top dose of Qsiva, the majority of these events were of mild severity, occurred early in treatment, resolved spontaneously or with discontinuation of study drug, and did not result in significant medical sequelae. Importantly, incidence of depression, anxiety, and insomnia were similar between placebo and the mid dose, respectively. On the basis of these effects, appropriate warnings and measures have been incorporated in the SPC and the RMP. Also, the Applicant has committed to conduct a dedicated clinical study to further elucidate cognitive effect of Qsiva in the target patient population, see the previously provided study OB-407 draft synopsis.

Ground 3

Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard to the teratogenic risk of the product when used in a less controlled real life setting.

Grounds for re-examination, applicant's position:

Although the potential increase in risk for certain birth defects (cleft lip, palate) has been associated with the use of topiramate, no causal relationship has been established to date. Topiramate has been approved for 16 years and is currently in widespread use within the EU for migraine prophylaxis – an indication comprised largely of women of reproductive potential, and for epilepsy, which requires treatment at higher doses, and in some cases, continuation of treatment throughout pregnancy. There is, therefore, a long history regarding the potential teratogenic risk of topiramate when used in a less controlled, real world setting. In this environment, topiramate currently does not have a RMP and patients may be able to receive up to three months of drug supply with each prescription or refill. The SPC for topiramate does, however, contain language contraindicating its use for migraine prophylaxis in women of childbearing potential who are not using adequate contraceptive measures, and similar SPC language has been accepted by the Applicant for the labelling of Qsiva, and is appropriately reinforced in the healthcare provider checklist of the Qsiva RMP.

During the review of this application, the Applicant submitted data showing the number of topiramate-exposed pregnancies through November 2011, as reported by the EURAP registry along with the number of topiramate prescriptions in the EU, as ascertained from the SDE Physician Drug and Diagnosis Audit. To help describe the effect of topiramate labelling on minimising pregnancy exposures, similar data were also shown for lamotrigine, another antiepileptic drug, but one without similar contraindications against use in pregnancy. Results from these data sources indicated that the number of exposed pregnancies per prescription in women of child bearing potential was 10-fold lower with topiramate as compared to lamotrigine, indicating that restrictive labelling is demonstrably effective in preventing pregnancy exposures in a real life setting.

Since phentermine is a controlled substance, it is expected that patients treated with Qsiva will only be able to obtain a 30-day supply of drug with each prescription or refill. Accordingly, educational materials specifically warning of risks to the foetus with exposure during pregnancy and promoting the need for adequate contraception will be delivered with the medication to appropriate patients on a monthly schedule. The monthly delivery of these messages will have the effect of strengthening a system that has already been shown to work in the commercial setting.

The steps proposed by the Applicant for management of the risk of teratogenicity with Qsiva represent a reasonable strengthening of risk minimisation measures that have already been shown to be successful, effective and proportionate, and will provide adequate assurance on safety without being unnecessarily burdensome for patients or prescribers.

Ground 4

The probability of off-label use of this product outside the population covered by the claimed indication is expected to be high. The risk minimisation measures as proposed by the applicant to limit such off-label use were considered difficult to set up in practice.

Grounds for re-examination, applicant's position:

The Applicant accepts the comments raised by the Pharmacovigilance Risk Assessment Committee (PRAC) regarding the feasibility and proportionality of some of the features of the proposed restricted prescribing/distribution/dispensing program for this type of product.

To address these concerns, the applicant is proposing to retain restricted prescribing (to physicians experienced in management of obesity and/or obesity-related co-morbidities) but remove the mechanisms for restricted distribution (to attested pharmacies) and dispensing (in the pharmacy, requiring the Prescriber/HCP Checklist). The Prescriber/HCP Checklist will be retained as a useful educational/reminder tool, but it will no longer be linked to restricted dispensing. The other educational materials (Prescriber/HCP Educational Guide and Patient Education Card) will also be retained.

The Prescriber/HCP Checklist and Prescriber/HCP Education Guide will encourage appropriate prescribing. Although the RMP has been substantially simplified, the proposed measure exceed those of an average RMP and it remains robust and proportionate for Qsiva, taking into consideration the potential exposure and setting in which the medicinal product will be used.

Of the three-part system originally proposed, the restricted prescribing would have been the most important component, as well as being applicable across the EU-27 countries, encouraging the use of Qsiva according to the approved label at the time of prescription. As such, of the three previously proposed restrictions this is the key component to retain and will ensure appropriate usage of Qsiva, addressing the risk of off-label use in an effective manner.

Coverage and usage of the Prescriber/HCP Checklist will be one of the centrepieces of the Qsiva educational program and will also be encouraged by a communication plan (initial HCP risk minimisation information letter as well as periodic communications at 6-monthly intervals from Qsiva EU launch, both for new prescribers and as a reminder for existing prescribers, with a review after 2 years). In addition, the use of the Prescriber/HCP Checklist will be optimised by availability of the tool via multiple channels, by the web, and also by a paper-based checklist as a back-up mechanism.

The applicant is therefore proposing to remove the restricted dispensing mechanism since this change significantly simplifies the implementation of the proposed risk minimisation activities, addressing the feasibility concern. Regarding the concern over the proportionality of the restricted prescription/distribution and dispensing mechanisms for this type of product, the applicant is also proposing to remove the controlled distribution mechanism from the risk minimisation, thus further increasing the ease of implementation and applicability across all member countries.

The wording of the SPC section 4.4 (Special warnings and precautions for use) will be updated to reflect this change, as follows:

> *"In order to ensure a positive benefit/risk balance, Qsiva is subject to a Risk Minimisation Plan across the European Union. Specifically, Qsiva should be prescribed by physicians experienced in the management of obesity and/or obesity-related co-morbidities using a specific prescriber checklist. The checklist should be utilised at initiation of therapy, 3 and 6-months post-initiation and also at 3 months after up-titration if the top dose is used."*

Although a restricted dispensing mechanism will no longer be employed, there will still be some additional mitigation of dispensing hazards. An awareness communication will be sent with the first supply of Qsiva to each pharmacy, with information that an HCP Education guide is available (online through a web-based portal and also in a hard copy as a back-up); this will encourage pharmacists to dispense Qsiva in an appropriate manner.

The effectiveness of the individual risk minimisation tools and overall risk minimisation approach will be evaluated post-launch, as described in section 4.3.2 of the RMP. Effectiveness will be assessed at five different levels and the evaluation will highlight not only the overall effectiveness of the risk minimisation approach but also the level of effectiveness of the individual risk minimisation tools. If, following periodic evaluation against target percentage rates for each evaluation metric, modification to the risk minimisation approach or tools is needed, changes would be made in a timely manner.

The updated RMP also includes an enhanced EU patient registry, entry into which will be possible by the web-based checklist, as well as directly through paper and telephone enrolment. The proposed updates include enhanced surveillance of cardiovascular, psychiatric and teratogenic risks through a targeted questionnaire at 6-monthly intervals. Awareness of the registry will be raised through improved communication at launch and also periodic intervals via additional communication channels, including journal adverts.

The aims of the registry will be to obtain further information on the benefit-risk profile of Qsiva, as well as assessment of the effectiveness of the RMP overall. A separate drug utilisation study (DUS) in selected EU countries which have pre-existing pharmacist prescribing databases will be used to assess the extent of off-label prescribing, and incorporate a poison centre study performed in a range of EU countries to provide data on overdose and abuse potential. An overview of the patient registry and DUS protocols is provided in section 2.4 of the RMP.

Additional expert consultation - Report from the SAG

1. Qsiva is associated with a dose-dependent increase in heart rate, mediated by the sympathomimetic properties of phentermine, but not accompanied by an increase in blood pressure. Subject to measures to minimise the risks (contraindication in patients at high cardiovascular risk, warning in SmPC regarding monitoring of heart rate and basis for discontinuation, and proposed post-authorisation cardiovascular outcome study), is the long-term cardiovascular safety profile of QSIVA sufficiently characterised, manageable and considered acceptable if weighed against the expected benefit?

The applicant clarified during the discussion with regard to heart rate increase, that the greatest increases in the <60 / 60-90 / >90 categories were seen in the <60 bpm group, thus alleviating concerns by one expert with patients with autonomous neuropathy and typically elevated baseline HR. With regard to the mechanism of the BP-lowering effect of Qsiva, the applicant stated that this was a very early effect well ahead of the bulk of the weight loss, which may be related, however, to decreased caloric intake and initial weight loss as well as an early diuretic effect.

Question 1 was then discussed by the SAG extensively. The view among the 3 cardiologists attending the SAG meeting with regard to whether the available data was sufficiently reassuring regarding the long-term cardiovascular safety profile was divergent: One cardiologist was not much concerned about the small average increase in heart rate; he stated, however, if there would be a risk of valvulopathy, this was a major concern. Therefore, he recommended to include echocardiography in the proposed CV outcome study, but also to address the potential issues of heart rate increase and its detrimental effect with regard to heart failure. Another cardiologist was not reassured by the available data for use of Qsiva both in the long- and in the in the short-term, and the third cardiologist had some concerns about the possible long-term consequences of the sympathomimetic effect of Qsiva. One cardiologist pointed out that the relatively high rate of arrhythmias would be due to inclusion of e.g. palpitations etc. as MEDRA terms. Interactions with beta-blockers and statins were raised as an issue. Two out of three cardiologists agreed that there were no concerns with regard to use over a period of time as in the clinical development program.

One expert pointed out that there are numerous drugs on the market which increase heart rate, and that as such would not necessarily constitute a concern. Experts were concerned with those subgroups in the studies, where HR increased substantially (i.e. more then 10, 15 or 20 bpm) and suggested that this could be further taken into account specifically in risk management and studies.

A number of experts were not concerned about the cardiovascular safety profile to the extent that would preclude its use based on the currently available data, in particular if the dose range would be restricted to the mid dose. However, at least two experts were of the view, that the current characterisation of the CV safety profile would preclude any use at this time, since it would be usually used as a long-term treatment of unknown duration, and since it would be not possible to have any view of the long-term CV safety due to the very small MACE event rate in the underlying clinical development program and the principle concern with regard to the mechanism of action of phentermine.

There were several comments about the proposed CV outcome study: it was suggested by individual experts to consider an interim analysis to include ECGs, echocardiography and more parameters of benefit other than CV parameters.

Overall, with some dissenters, the SAG was of the view that the CV safety profile with regard to the use over a period of time as in the underlying study data (i.e max. 2 years, considered here as "long-term" by the SAG) could be acceptable, in particular when restricted to the mid dose as a maximal dose and with the caveats outlined above. The SAG felt unable to give a view on the safety profile beyond this time span.

2. Adverse psychiatric effects (depression, anxiety, and cognitive impairment) were more common in subjects treated with Qsiva, notably at the high dose, but generally occurred early in treatment and were reversible on discontinuation. Subject to warnings concerning initiating treatment in those with a pre-existing history, a requirement to re-evaluate the benefit-risk balance after three months and before titration to the high dose, and amendment of the patient education materials, are the psychiatric risks considered acceptable in comparison with the expected benefits of treatment?

In the discussion with the applicant one psychiatry expert raised a concern with the apparently low baseline rate of depression in the study, thus questioning the validity of the measurement tools. Another concern was by an expert that patients not uncommonly seen in specialised outpatient clinics with BMI in the range of 50 or 60 kg/m^2 have a very high rate of psychiatric morbidity, but only very few of those patients were included in the clinical study program. This was acknowledged by the applicant but who also pointed out that the program did include studies with no upper limit of BMI as exclusion criterion unlike some historical clinical programs with upper limits of ≤ 45 kg/m^2.

One psychiatrist raised as a concern that the measurements used by the applicant in the studies were only suitable as screening tools but not as diagnostic tools for psychiatric conditions. Another psychiatrist had concerns with the abuse potential of Qsiva, even though that it would be expected to be less than with phentermine alone. A psychiatrist also suggested to include major psychiatric illnesses (in particular anxiety, depression) as contraindications, and to mandate a full psychiatric evaluation before treatment.

For several of the participating other experts, the adverse psychiatric effects profile posed the biggest concern with the use of the product. Some experts in particular raised concern, whether at time of prescription the involved doctor(s) may have sufficient psychiatric knowledge with that regard.

Therefore, the SAG was of the view that prescription should be restricted to specialised services, preferably with access to an interdisciplinary team. It was acknowledged that the precise

requirements for this may be variable from country to country, and that it may be problematic in countries with less such resources. Principle treatment should be restricted to doctors with expertise in obesity (although quite difficult to delineate and which may be in some countries endocrinologists, diabetologists, or specialised internists) with other specialists, such as cardiologists and psychiatrists, involved as part of a multidisciplinary team. From the patient representatives there was one view stating that he was quite concerned about the psychiatric adverse effects profile, and the other stated that the drug should be made available in specialised centres only with access to a psychiatrist. Overall, the SAG was of the view that wherever the product would be prescribed, the availability of sufficient psychiatric expertise would need to be ensured, and that would be preferably in multidisciplinary centres. With the caveats as outlined above, the SAG was of the view that the psychiatric risks could be acceptable.

3. The Applicant proposes a post-authorisation study in 120 subjects to investigate the cognitive effects of Qsiva following 24 weeks of treatment. Does the SAG consider that the design and duration of this study is appropriate?

The attending psychiatry experts found that the test battery and overall design of the proposed study is adequate. It was felt that this was a relevant study as the combined use of phentermine and topiramate had not been specifically tested with regard to cognitive effects. It was mentioned, however, that repeated use of neurocognitive test batteries may lead to learning effects and that a longerterm follow-up of participants would be desirable.

4. Pregnancies have been reported in rather high numbers in the clinical trial program. Given the large target market for Qsiva in young obese women, does the SAG consider that the teratogenic risk of the product when used in a less controlled real life setting may be sufficiently minimised with the enhanced pregnancy prevention measures proposed?

The SAG was very sceptical about the success of the proposed measures. Most participating experts doubted the long-term adherence to the required measures (i.e. two pregnancy-preventing methods for women with child bearing potential, etc.). Only a small minority of the participating experts was of the view that the proposed program would ensure sufficient long-term pregnancy prevention or that the issue was not a concern. One of the patient representatives was of the view, that those concerns alone, however, should not preclude the availability of the product.

5. The probability of off-label use of this product outside the population covered by the claimed indication is expected to be high. Please comment on the feasibility of the measures proposed to minimise the risk of off-label use (restricted prescribing, educational material for prescriber and patient, and drug utilisation study).

Several experts pointed out that this product was a product which a significant number of individuals would have a high desire to obtain regardless of being indicated or not. As such, many experts doubted that the proposed measures would ensure this not to happen, either at the level of the prescriber or otherwise. The SAG felt, this was another reason to recommend restricting the prescription of the product to specialists (see also response to question 2). One expert highlighted that he did not expect that educational material will prevent non-indicated prescription and use.

Overall, the SAG agreed that the proposed measures were unlikely to suppress off-label use, and there was an evenly split opinion by the SAG whether this nevertheless could be acceptable (given that individuals may obtain the product, even if not marketed in the EU) or whether the ensuing expected high rate of off-label use would be unacceptable.

6. Does the SAG consider that the benefit-risk profile would be more favourable if only the low and mid doses were licensed, in view of the dose-related nature of the adverse events?

The SAG felt this clearly to be the case. Two participating experts dissented, since they felt the low and mid dose to have an equally negative benefit-risk profile as the high dose.

7. Can the SAG identify an appropriate population in terms of BMI and relevant co-morbidities?

With regard to further defining a suitable population for treatment with Qsiva, the experts had various views such as: to simplify and restrict to BMI only as criterion, e.g. a BMI of ≥ 35 kg/m^2; to restrict to diabetes patients with a BMI of ≥ 30 kg/m^2 (but it was felt inappropriate to exclude the important group of patients at risk to develop diabetes such as those with impaired glucose tolerance); a BMI of ≥ 30 kg/m^2 and some selected co-morbidities; a scoring system (instead of BMI, which was felt by one expert to be too narrow as criterion). Two experts were in favour of maintaining the currently proposed indication wording.

Overall, the SAG agreed that, independent of approvability of the product for other reasons, the target population should in any case be further restricted. The SAG was not able to come up with a consolidated majority view of a new more limited indication wording, but has instead offered some individual views as listed above.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4, the PRAC considered by consensus decision that the risk management system for phentermine / topiramate (Qsiva) is not acceptable since the proposed pharmacovigilance and risk minimisation activities are not adequate for the following reasons:

Long term cardiovascular effects

Pharmacovigilance Plan

PRAC considered that the proposed protocol for the randomised controlled trial aiming to gather further data on the long term cardiovascular effects of Qsiva was deficient in a number of aspects:

- insufficient consideration had been given to difficulties recruitment, discontinuations and compliance taking into consideration the number of protocol-driven investigations required over the duration of the trial. (PV Plan)

- the only proposed reporting milestone for the cardiovascular outcome study was the final report to be submitted to the EMA on study completion. Provision should be made for the reporting of interim results given the long term nature of this trial. (PV Plan).

- the proposals for ECG and echocardiography were insufficient to enable early identification of valvulopathy or pulmonary arterial hypertension.

Risk Minimisation measures

Additional risk minimisation measure is necessary for monitoring of heart rate and blood pressure prior and throughout treatment.

Psychiatric disorders

Pharmacovigilance Plan

The details provided in the registry protocol raised concerns about the adequacy of data capture of psychiatric reactions.

The use of a standard questionnaire in the CV outcome study would not capture sufficiently robust data on treatment emergent psychiatric adverse effects.

The cognitive effects study needs to include a larger sample size due to possibly high drop-out rates and a prolonged follow-up of patients to ensure enough exposure time on allocated doses should be considered.

Risk Minimisation measures

PRAC recommended that as an additional risk minimisation measures, the stopping criterion should be broadened to ensure that the decision to continue treatment beyond month 3 is based upon an assessment of the benefit-risk balance rather than just response to treatment.

Teratogenicity

Pharmacovigilance Plan

PRAC considered that although the focus should be on preventing pregnancies, for those pregnancies that do occur, complete data on outcomes is necessary and the registry protocol did not adequately ensure complete capture of these data.

Risk Minimisation measures

PRAC considered that the proposed risk minimisation measures with regards to teratogenicity were insufficient and recommended the need for a Pregnancy Prevention Programme (PPP), the principles of which should be consistent with that agreed across the EU for isotretinoin in 2003.

Off-label use

Pharmacovigilance Plan

The PRAC noted the registry is a key component of the applicant proposals to gather long term data on the safety of Qsiva and minimise off-label use and considered that this registry should be of a compulsory nature and a condition for prescription.

PRAC considered the proposed DUS study from the applicant to be inadequate as it did not involve a sufficiently larger number of countries representative of the EU population.

Risk Minimisation measures

PRAC considered that the proposed educational materials and patient safety card were deficient as they did not adequately capture all key risks.

Conditions or restrictions regarding supply and use

PRAC considered that restricting prescribing to clinical settings where prescribing decisions can be informed by a multi-disciplinary clinical team that can assess both the physical and mental health of the patients and the appropriateness of treatment with Qsiva are needed to minimise the risks.

Overall, PRAC considered that individual risks could potentially be adequately characterised and managed in isolation. However, in light of the indication, the envisaged benefits of treatment and the clinical setting the cumulative burden on both the prescriber and the patients of the necessary risk minimisation measures were considered inappropriate and extremely difficult to maintain in the long term.

The CHMP endorsed this advice without changes.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group and the advice from the PRAC.

In the view of the CHMP an unmet medical need in the treatment of patients with obesity is acknowledged. Qsiva has proven to be very effective in reducing body weight, with a mean weight loss from baseline of approximately 8 and 10% for the mid and high dose, respectively, in the first year. However, no additional weight loss was seen in the second year, rather there was a mean weight gain in all groups. Reduction of weight can be assumed as surrogate parameter for a beneficial cardiovascular (CV) outcome and current EMA guidance on medicinal products used in weight control does not require demonstration of a positive effect on CV morbidity and mortality prior to approval. However, weight reducing agents with a mechanism of action with a detrimental influence on heart rate, such as Qsiva, or on other cardiovascular parameters, may require further exclusion of a harmful CV effect.

1. Cardiovascular safety – The CHMP had methodological concerns with regard to the quality of the data source (with dropout rates of about 40%, and lost to follow up rate above 10%) and the magnitude of the dose-dependent increase in heart rate (as heart rate measurement was not an end point in the Qsiva clinical program and no standardised methodology for accurate assessment was implemented). The Applicant presented hazard ratios for major cardiovascular events in Qsiva-treated subjects. Although these showed no obvious increased frequency of events with treatment, the data are of limited value as the duration of follow-up was relatively short and the total number of events was small. Therefore, the lack of power, and thus reliability, of the post-hoc analysis of cardiovascular events during the Qsiva clinical development program remains a major concern, since with a total number of 1526 patients of low CV risk treated for one year the expected rate of CV events is extremely low and thus of little significance for the assessment of the CV risk. In the view of the CHMP, any increase in heart rate can remain a concern with regard to CV risk. Estimates of the mean heart rate were considered by CHMP not to be necessarily the most relevant parameter (compared to e.g. increase in heart rate in the highest percentile or increased proportion of subjects with > 10 bpm) The consequence of the sympathomimetic mechanism of action of Qsiva for CV outcome in long-term use remains a principle concern for CHMP in the absence of long-term CV outcome trial data. The supportive information on safety of phentermine from the literature provided by the applicant was considered by CHMP to be very limited due to factors such as only retrospective, cohort studies submitted, absence of a reliable control group, etc. Although the amount of phentermine in the high dose of Qsiva is half of that currently licensed for use as a single agent in the US and the UK, the addition of topiramate was shown to increase exposure to phentermine by 40% in the PK studies. Therefore the cardiovascular effects of Qsiva cannot be implied from data for higher doses of phentermine as a single agent.

2. Psychiatric safety – Depression, anxiety and cognitive impairment were more commonly reported in patients treated with Qsiva than placebo. The collection of psychiatry data with screening instruments such as QPH-9 and C-SSRS was found by CHMP to be inadequate since diagnostic instruments are

more powerful and would be needed to reliably establish the clinical relevance and magnitude of the psychiatry adverse events (AEs) observed with Qsiva. Dropout rates for depression with Qsiva significantly outnumbered those with placebo; thus close surveillance in trials may have stopped progression to more severe symptoms. The applicant's claim that by applying the 3 month stopping rule for non-responders, the number of drop-outs due to neuropsychiatric AEs in the Qsiva group would not exceed those in the placebo group was questioned by CHMP. With regard to reported cases of suicidal ideation in patients treated with Qsiva during the clinical studies, regular assessments in this regard would be required. Another concern was the feasibility to exclude patients with moderate depression from treatment. Overall, the availability of psychiatric expertise at sites of treatment with Qsiva was considered to be necessary by CHMP.

During the re-examination procedure, the applicant proposed a further revised SmPC which forgoes the top dose of Qsiva, associated with the highest rate of psychiatric and cardiovascular adverse events. While the CHMP acknowledged that this could improve the benefit/risk ratio, CHMP concluded that the proposed removal of the high dose from the application did not sufficiently alleviate the concerns of the CHMP both with regard to the psychiatric and cardiovascular safety profile (see points above), which remains for the lower doses. Additionally, the Committee noted that the actual patient numbers treated with the recommended mid dose were limited.

3. Teratogenic risk - CHMP agreed that the risk from the teratogenic potential of Qsiva might be mitigated through the implementation of appropriate risk minimisation measures, which include a Pregnancy Prevention Plan (PPP), the principles of which should be consistent with that agreed across the EU for isotretinoin in 2003. However, it was recognised that effectiveness of the PPP in clinical practice will be difficult to maintain in the long-term use.

4. Off-label use - The CHMP considers that Qsiva is expected to have a high probability of off-label use, particularly in patients with some nutritional disorders (e.g. bulimia, Binge Eating Disorder) as well as in psychiatric patients, paediatric populations, adults with high CV risk, and elderly patients. There remains uncertainty whether off-label use can be sufficiently mitigated by the measures proposed by the applicant. The applicant's proposal to retain restricted prescribing (to physicians experienced in management of obesity and/or obesity-related co-morbidities) but to remove restricted distribution and dispensing requirements remained a concern to CHMP as this may still represent a broad prescriber base not limited to specialists. The proposed patient registry was considered a key component to gather long term data on the safety of Qsiva and on the effectiveness of the risk minimisation measures, especially in relation to off-label use. However, due to the voluntary nature of the registry the expected participation was considered to be low and hence its capacity to minimise off-label use remained uncertain.

The CHMP further considered that restricting prescribing to clinical settings where prescribing decisions can be informed by a multi-disciplinary clinical team that can assess both the physical and mental health of the patients and the appropriateness of treatment with Qsiva could help minimise the risks but had concerns about the feasibility of this practice in all EU member states.

In conclusion, following assessment of the detailed grounds for refusal including the revised risk management proposals provided by the applicant, the CHMP concluded that the safety of the above mentioned medicinal product is still not sufficiently demonstrated.

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, in the treatment of

Obesity, including weight loss and maintenance of weight loss in adults, as an adjunct to reduced calorie diet and physical activity. QSIVA is recommended for obese patients (BMI ≥ 35 kg/m^2), or obese patients (BMI ≥ 30 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidemia. QSIVA should only be prescribed by specialist physicians experienced in the management of obesity.

the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the safety of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

1. The long-term cardiovascular safety of Qsiva has not been sufficiently established. Phentermine's mechanism of action is of concern as it has sympathomimetic properties inducing cardiac stimulation and its use is associated with an increase in heart rate. It is only being approved for short-term periods of treatment (less than three months) and its long-term cardiac toxicity is unknown. Existing data from phentermine use has major limitations and cannot be extrapolated with regard to conclusions on the safety profile of Qsiva. The proposed removal of the top dose for the use of Qsiva does not alleviate the concerns. The currently available cardiovascular outcome data for Qsiva remains inconclusive;

2. The frequency of adverse psychiatric effects and their consequences, in particular resulting from the topiramate component, is unknown in the setting of long term use of this product in a large population. In addition, the cognitive effects of such combination during long term treatment remain uncertain in absence of adequate studies;

3. Pregnancies have been reported in rather high numbers in the clinical trial program raising concerns with regard;

4. The probability of off-label use of this product outside the population covered by the claimed indication is expected to be high. There is remaining uncertainty whether the updated risk minimisation measures as proposed by the applicant could effectively prevent such off-label use.

Divergent position to the majority recommendation is appended to this report.

APPENDIX

DIVERGENT POSITION

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Qsiva.

The reasons for the divergent opinion were as follows:

According to literature and the CHMP guideline, the loss of at least 5 to 10% in body weight is associated with beneficial effects on several cardiovascular risk factors and is accepted as a surrogate for reduced cardiovascular risk as well as reduction in the risk of development of type 2 diabetes. The proportions of patients achieving these endpoints after 12 months of Qsiva treatment were 62 and 38%, respectively, with the mid dose 7.5/46mg. These beneficial effects of Qsiva, with respect to weight reduction, are considered as being of high clinical importance, being substantially larger compared to previous and current alternatives. This could be of specific importance in subjects with severe obesity, e.g. with a BMI ≥35 kg/m^2, for whom few treatment alternatives exist and who could be expected to experience greater benefits. In these patients, Qsiva would fulfil an unmet medical need. Further, QSIVA treatment has been shown to have a positive effect on other cardiovascular risk factors such as blood pressure, waist circumference, serum lipids and HbA1c. Available data showed that the effect of the mid dose is maintained over 2 years of treatment.

The incidence of depression and anxiety was increased significantly only with the high dose of QSIVA, but not with the mid dose, which is the recommended dose. Information and recommendations concerning monitoring for these effects is included in the proposed product information, educational material and prescriber check list, together with warnings regarding treatment of those with a previous history. A proposal is also included to further evaluate cognitive effects over the longer-term in the post-authorisation setting.

Due to its mechanism of action, phentermine may lead to an increase in heart rate. However, no significant increase was seen with the mid dose. With the high dose the mean increase was 1.6 bpm. There was a reduction in baseline blood pressure observed with the mid and high dose levels. There were no indications of an increased risk of major cardiovascular events in the submitted studies. The impact of a possible increase in heart rate in obese patients will be evaluated in a large, post-authorisation, cardiovascular outcome study.

Considering the known teratogenic potential of topiramate in the context of the target population, largely consisting of fertile women, measures to avoid pregnancy are of importance. A comprehensive pregnancy prevention plan is set out within the SmPC, which when combined with a contraindication for women of child bearing potential who are unable or not willing to use adequate contraception during treatment, should serve to minimise the risk of exposure during pregnancy. Similar strategies have previously been acceptable within the EU for products with a greater degree of teratogenicity. The proposed RMP has been updated to include comprehensive prescribers' and subjects' medication guide, and the teratogenic potential of topiramate is reflected in the proposed SmPC. A maximum prescription of 30 days supply is suggested for these women to facilitate regular pregnancy testing.

Most of the reported adverse events were dose dependent. The highest dose was removed from the application by the Applicant, and the reporting rates of adverse events for the mid dose were not significantly higher than for placebo-treated subjects. Furthermore, only patients who achieve a ≥5% weight reduction after 12 weeks treatment, and tolerate therapy, should continue on Qsiva.

Further proposed risk minimisation activities include a patient registry to capture and monitor adverse events related to the identified and potential risks; a drug utilisation study to evaluate prescription patterns and records of abuse; and a proposal to restrict prescription to specialists experienced in the management of obesity.

In conclusion, the weight lowering effect of Qsiva is considered to be of high clinical relevance, being considerably larger than that observed with current treatment alternatives. Scientific literature supports the link between this effect and improvements in cardiovascular risk and longevity. Benefits in orthopaedic conditions, sleep apnoea as well as psycho-social benefits could also be expected. Qsiva is proposed to be recommended for obese patients (BMI ≥ 35 kg/m^2), or obese patients (BMI ≥ 30 kg/m^2) with weight-related co-morbidities such as hypertension, type 2 diabetes or dyslipidaemia, i.e. a population with a high medical need. With the proposed measures in the SmPC and the RMP, the safety issues are considered manageable. The benefit/risk balance is therefore considered as positive.

London, 21 February 2013

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