SCIENTIFIC DISCUSSION

1. Introduction

Obesity is a chronic and highly prevalent illness which is frequently associated with numerous and sometimes fatal diseases. It is a complex disease of multifaceted aetiology (including environmental factors and genetic predisposition), with its own disabling capacities, pathophysiology and comorbidities. Some of the complications of obesity include type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, arthritis and cancer.
Non-pharmacological options for treatment include nutritional education and modification (usually caloric restriction), behaviour modification, and increased exercise. In severe obesity, very low caloric diets and surgery may be used. Pharmacological options are only considered as an adjunct to dietary measures. There are a few antiobesity agents available. They can be divided into centrally acting anoretic agents and drugs that inhibit the absorption of nutrients. There are numerous symptomatic treatments of the metabolic complications of obesity (antihypertensive drugs, hypolipedemic agents, antidiabetic drugs).

Smoking is a well-known risk factor for the development of cardiovascular disease, chronic obstructive pulmonary disease, and lung-cancer and therefore represents a major public health concern. Approximately 1.3 billion people currently smoke worldwide and smoking is estimated to be responsible for 4.9 million premature deaths each year, a figure expected to nearly double by 2020. Many people have difficulty with quitting, nicotine dependency being strong. In addition to counselling programs, there are several options for pharmacotherapeutic intervention: nicotine replacement therapy (NRT), and bupropion (Zyban®). The latter, originally developed as antidepressant, is a noradrenalin, dopamine, serotonin re-uptake inhibitor and a non-competitive nicotine receptor antagonist. Both are marketed as an aid to smoking cessation, and have an efficacy rate of approximately 20-30% abstinence at an average of 3 months treatment.

Rimonabant is a selective antagonist of cannabinoid type 1 (CB1) receptor. Rimonabant is the first member of a new class of compounds that target a novel physiological system, the endocannabinoid system (ECS). The cannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes.

The proposed indications for rimonabant were: Management of multiple cardiovascular risk factors, weight management, type 2 diabetes, dyslipidaemia, smoking cessation and maintenance of abstinence.

In adults, the recommended dosage is one rimonabant 20 mg tablet daily to be taken in the morning before breakfast. Rimonabant has not been studied in patients less than 18 years old.

This application was a complete and independent application concerning a new active substance according to article 8.3 (i) of Directive 2001/83/EC.

2. Quality aspects

Introduction

ZIMULTI is presented as film-coated tablets containing 20mg rimonabant INN. The product is packaged in PVC-aluminium blisters and in HPDE bottles closed with a child-resistant tamper-proof polypropylene screw cap.

Active Substance

Rimonabant is a fine powder, white to practically white. Two different polymorphic forms (1 and 2) have been identified during development. Form 1 has been used from the beginning of the pharmaceutical development to the end of Phase 3 clinical studies. Form 2, identified after the start of Phase 3 studies, was selected for product development. The two forms have very similar physico-chemical characteristics. As rimonabant is practically insoluble in water, the drug substance has been micronized to increase particle surface area and thus, facilitate dissolution, and to ensure blend homogeneity during drug product manufacture.

- Manufacture

The quality information in Module 3 of the dossier has been supplemented by detailed confidential information on the synthesis of rimonabant in the Restricted Part of an active substance master file (EDMF, ASMF).

Acceptable specifications on starting materials, intermediate, solvent and reagents have been presented (in the restricted part). The submitted data are considered to be acceptable.

Process impurities originating from each of the starting materials and from synthesis have been adequately discussed. Organic impurities have been synthesised and characterised by spectroscopy. The presence or absence of impurities has been examined by spectroscopy and/or chromatography in all batches, including those used in toxicology and clinical studies.

Crystallisation studies confirm that polymorphic form 2 is routinely produced by the synthesis.

- Specification

The specification includes relevant tests for assay (HPLC) related impurities, residual solvents, etc.
In addition, the particle size distribution is also specified (laser granulometry).
The final specification for rimonabant is based on batch analyses for three consecutive industrial scale batches, several toxicological and clinical batches, and stability data. The analytical methodology has been validated to meet the requirements of the ICH guideline Q2B, Validation of Analytical Procedures.

- Stability

Data from primary stability studies in the solid state demonstrate that under stress condition, rimonabant is stable to high temperature and/or humidity, but is very slightly sensitive to intense light. In hydro-alcoholic mixture, rimonabant is stable at 80 ºC, but is sensitive to light and to oxidants.

Three pilot scaled batches of form 2 have been stored in the proposed packaging for routine storage for at least 12 months at 30°C/65% RH and 6 months at 40°C/75% RH.
No significant changes in the results of the routine tests for appearance, water content, related substance, assay and polymorphic form were observed for any of the batches for the reported duration of storage up to 12 months and 6 months respectively. There is no significant formation of impurities The assay results remain within specification and X-Ray studies indicate there is no change of the polymorphic form. The proposed re-test period of 24 months is considered to be acceptable.

Medicinal Product

- Pharmaceutical Development

The development of the finished product has been well performed and explained and is satisfactory.

The permeability of the drug substance has been determined in Caco-2 cells at pH 6.5 and is found to be high. Rimonabant is therefore classified as a Class 2 substance considering solubility and permeability properties, according to the Biopharmaceutics Classification System (BCS).
However, considering the low solubility, both particle size and physical form are controlled.

The excipients are commonly used in medicinal products for oral use. Also the packagings are usual and suitable for the product.

The phase 2B and phase 3 clinical studies were performed with capsules containing Rimonabant polymorphic form 1, whereas the commercial product is a tablet containing rimonabant polymorphic form 2. These differences in dosage form and polymorphic form have been explained and justified with 'bridging' bioequivalence studies. The bioequivalence studies demonstrated that there is bioequivalence between the film-coated tablets intended for marketing and the hard capsules used in Phase 3 studies, independent of polymorphic form or solid dosage form when the dissolution profiles in pH 6.2 are similar.
In addition, during further development the colour of the coating changed from blue (indigotoxin) to white (titanium dioxide). The tablets cores remained identical and, except for the dye, the coating formulation also remained the same. These differences are considered to be minor and of no clinical significance in the satisfactory performance of the marketed product.

- Manufacture of the Product

A standard process of wet granulation is used. This has been validated and optimised with regard to a number of variables.

- Product Specification

The release specification includes relevant tests with validated methods and limits for appearance and identification, assay (HPLC), uniformity of content, degradation products, dissolution, microbiological purity etc.
The shelflife specification is identical with regard to assay (no change).
Batch analyses confirm the satisfactory uniformity of the product and indicate the manufacturing process is under control.

- Stability of the Product

The tablets intended to be marketed have been studied at 30°C/65 % RH and 40°C/75 % RH. In addition, results from studies on prototype formulations not intended for the market have been used as supportive data.

No significant changes in the results of the routine tests for characters, dissolution, assay and degradation products were observed for any of the batches for the reported duration of storage.

The tablets were also evaluated for their photostability according to ICH Q1B. The results of this study conducted under intense light demonstrate that the product is stable: No degradation products are formed,

and dissolution is unaffected. In general the results support the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

In general satisfactory documentation has been provided to confirm the acceptable quality of this medicinal product, and no major objections have been raised during evaluation. The drug substance is adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. The solid drug substance is stable with respect to degradation.

Concerning the finished product, the release specification and in-process controls guarantee consistent control of the product quality. The drug product is stable with respect to degradation.

3. Non-clinical aspects

Introduction

Pivotal toxicology studies were performed according to GLP. External reviews of histopathological data were not always performed according to GLP. The safety pharmacology studies (conducted prior to guideline publication) were not conducted under formal GLP guidelines; the supplemental studies on vital functions were conducted according to GLP regulations.

Pharmacology

Rimonabant is a selective CB1 antagonist.

At present, two types of cannabinoid receptors have been characterized, CB1 and CB2. CB1 is widely distributed in the CNS with high concentrations in the basal ganglia, hippocampus, cerebellum, and parts of the limbic system. CB1 is believed to modulate the 'motivation/reward' system in the brain and to be involved in the regulation of appetite and drug addiction. There is evidence that CB1 is expressed peripherally, particularly on adipocytes, and that this receptor subtype may be involved in the regulation of lipolysis. Much less is known about CB2; this receptor subtype is expressed in lymphoid tissues but its function is currently unknown. Interaction of cannabinoids with other receptor types than CB1/CB2 have also been reported and it has been speculated that such 'non-classical' cannabinoid receptors may play a role for the physiological effects of endocannabinoids and other cannabinoid derivatives.

- Primary pharmacodynamics

Binding studies demonstrated that rimonabant is a potent (pKi 8.4) and selective ligand for CB1 receptors. It had a weak affinity to $Galanin_2$, MC_5, $opioid_\kappa$, and PCP receptors. Similarly, in enzyme interaction experiments with a variety of enzymes, rimonabant was found to activate COX_1 at 10 µM; no activation was seen at 1 µM. Functional in vitro studies confirmed its potent (pA_2 7.98 – 8.85) and selective CB1 receptor antagonistic activity.

Intraperitoneal administration of rimonabant reversed the inhibition of the isoniazid-induced increase in cerebral cGMP levels produced by cannabinoid agonist WIN55212-2 (ID_{50} value of 0.3 mg/kg), without affecting basal cGMP levels. Turning behaviour in mice induced by unilateral intrastriatal injection of WIN55212-2 was dose-dependently antagonized by rimonabant after oral or intraperitoneal administration (ID_{50} values of 0.22 mg/kg and 0.12 mg/kg, respectively). WIN55212-2-induced hypothermia and psychomotor effects in mice and rats, including ring-immobility and "pop-corn" effects in mice and barrel rotation in rats, were potently and dose-dependently antagonized by rimonabant

(administered either i.p. or p.o.; with ID_{50} values ranging from 0.2 to 1.7 mg/kg). The antagonism of WIN55212-2-induced hypothermia in mice by rimonabant (2.78 mg/kg, p.o.) was long-lasting.
In models for obesity, oral administration of rimonabant (1 and 3 mg/kg) caused a long-lasting and selective inhibition in sucrose drinking (75 and 70 %, respectively) and eating of a cane-sugar enriched (carbohydrate) diet. Repeated oral administration of rimonabant (3 mg/kg/day; for 12 days) also reduced the intake of the preferred high-fat diet (37 %) and the total energy intake in obese rats (by 30%). A marked decrease in body weight gain (93 %) was found in obese rats after 3 mg/kg/day of rimonabant. Similar (but less marked) effects were found in lean rats. The weight reducing effect of rimonabant (72 % after 10 mg/kg/day for 4 weeks in obese rats) was partly dependent on peripheral metabolic effects, possibly mediated by an increase in adiponectin secretion from the adipocytes. Rimonabant (10 mg/kg/day) also reduced known risk factors associated with obesity, including reduction of elevated levels of serum leptin (81 %), insulin (78 %), glucose (67 %) and restoring the lipid profiles (triglycerides, cholesterol, HDLc / LDLc ratio).

Rimonabant reduced nicotine self-administration at 0.3 mg/kg and cue-induced nicotine seeking at 1 mg/kg in the self-administration paradigm and at 3 mg/kg in the conditioned place preference test in several animal models.

- Secondary pharmacodynamics

The anxiolytic and antidepressant effects of rimonabant were assessed after a single oral administration at doses ranging from 10 to 100 mg/kg in male mice, using a battery of five tests. Rimonabant increased significantly the number of shocks (0.3 mg/kg) in the punished drinking test, as did diazepam (3 mg/kg). Rimonabant significantly increased percentage of time spent into open arms at 10 mg/kg in the elevated plus-maze test and did not affect the number of entries into closed arms; diazepam produced a similar effect at 3 mg/kg. Rimonabant significantly decreased immobility time from 3 mg/kg, p.o. in the forced-swimming test; fluoxetine produced a similar effect at 30 mg/kg. Finally, rimonabant slightly enhanced the sexual motivation of sexually naïve male rats but did not globally modify the copulatory behaviour of sexually experienced male rats.

- Safety pharmacology programme

Effects on the CNS (mouse, single oral dose) were particularly noted at dose levels ≥ 30 mg/kg. Single oral administration of rimonabant produced an increase in global activity followed by sedation and decreased body weight. These effects were more marked at 100 mg/kg, and associated at this dose level with decreased muscle tone and impaired motor coordination. A decrease in body temperature and in spontaneous motor activity was also observed at 30 mg/kg.

Rimonabant did not modify the threshold dose of pentylenetetrazole required to produce clonic convulsions, but showed a non-dose related propensity to potentiate tonic convulsive activity at dose levels ≥10 mg/kg in mice and increased mortality from 30 mg/kg. In view of these findings and of the convulsions observed in the toxicology studies with mice, rats and monkeys, the applicant was requested to study more in depth the proconvulsive activity of rimonabant. The results described in the literature and obtained by the applicant indicated a proconvulsant potential for rimonabant in animals when combined with physical or chemical seizures inducers, or with stressful conditions. Rimonabant had no effect on neuronal excitability in animals when administered alone. According to literature data, this proconvulsant effect was likely to be related to the blockade of an existing endogenous cannabinoid tone. EEG-data did not indicate any abnormality.

Other safety pharmacology studies suggested that at the dose-levels tested, rimonabant did not produce any major adverse effects on the cardiovascular, respiratory, renal and gastrointestinal systems. Electrophysiology findings included inhibition of the I_{Kr} channel in CHO cells transfected with hERG

(IC_{50} = 2.79 µM) and a prolongation of the action potential in isolated rabbit Purkinje fibres at 3 µM and higher. However, no QT prolongation or other ECG changes were seen in anaesthetised dogs after doses up to 100 mg/kg, i.d.

- Pharmacodynamic drug interactions

No non-clinical studies on pharmacodynamic drug interactions were carried out.

Pharmacokinetics

The metabolic fate and disposition of rimonabant were assessed in five animal species, i.e., mouse, rat, rabbit, dog, and macaque. Rimonabant was rapidly absorbed following oral administration, with peak concentrations occurring generally within 1 to 3 h after dosing in rats, dogs, and macaques. Oral bioavailability was low to moderate (12% in male rats, 46% in female rats, 18% in male macaques); this was due to extensive first pass metabolism. Rimonabant exposure increased in a dose-related manner in animals. A sex related difference in rats was noted; where female rats had higher rimonabant plasma levels than males, which was attributed to higher metabolism in males. Steady state pharmacokinetics generally occurred within 1 week during once-daily dosing.

The apparent volume of distribution of rimonabant following intravenous administration was larger than the total body water (0.7 L/kg) in rats (11.5 L/kg) and macaques (24.4 L/kg). Extensive tissue distribution of radioactivity was noted in rats, with transfer of radioactivity across the blood-brain barrier and also to the embryo and fetus across the placenta. The tissues with the greatest uptake were the liver, adrenals, brown fat, kidneys, lymph nodes; more than 3- fold accumulation following repeated once-daily doses was noted in the thyroid, spleen, plasma, thymus, liver, and brain. There was no uptake or retention in pigmented tissue (eye-melanin) of rats. Rimonabant was bound very extensively (up to 100%) to animal and human plasma proteins in vitro and did not distribute extensively into red blood cells. The extensive distribution in vivo in spite of the high plasma protein binding indicated a higher affinity of the drug-related material to tissues compared to plasma.

In all species, the metabolic pathways for rimonabant involved amidohydrolysis, multistep oxidative metabolism on the piperidine moiety, and further glucuronidation of the acid and hydroxy phase 1 metabolites. In plasma, SR141715-metabolite was the predominant metabolite in humans, mice, rats, and macaques. Since the formation of this metabolite was accompanied by the formation of N-aminopiperidine (NAP), a metabolite with genotoxic structural alert, further clarification on the formation and metabolism of this compound was requested by the CHMP during the procedure. In summary, the NAP-exposure after a therapeutic dose of rimonabant (20 mg/day) was estimated to be about 240 µg of NAP per day; the estimated exposures to NAP in rats and mice suggested that there were large margins to human exposure in the carcinogenicity studies (about 140-5000 in rats and 150-780 in mice, depending on gender and dose); there were no liver tumours in the mouse carcinogenicity study or in male rats, and the liver adenomas found in female rats could be explained by other mechanisms. These findings were reassuring. The applicant committed to further clarify the metabolic fate of NAP as a post-approval follow-up measure.

Rimonabant had a long terminal half-life in rats (7.3 h) and macaques (20 h) and a medium clearance in both species (~1 L/h/kg). Rimonabant and its metabolites were mainly excreted in the faeces (>70% of the radioactive dose) via bile, with only a small amount eliminated in urine in mice (<2%), rats (<1%), rabbits (7%), dogs (<1%), and macaques (<5%) after oral dosing. Rimonabant and/or its metabolite(s) were also excreted in the milk of the rats.

Repeated administration of rimonabant resulted in an increased CYP2B (and to a lesser extent CYP1A, 2C, 2E and 3A) activity in mice and rats, but not in macaques. In vitro studies with human hepatocytes did not demonstrate induction of CYPIA1, IA2, IIA, IIIA.

Toxicology

- Single dose toxicity

Acute toxicity studies were performed in both rats and mice using oral and intraperitoneal routes. In mice and rats, mortality occurred from day 4 or day 2 after oral or intraperitoneal administration, respectively. By the oral route, the observed maximum non-lethal doses were 1000 mg/kg in rats and female mice and 500 mg/kg in male mice. By the intraperitoneal route, the observed maximum non-lethal dose was 60 mg/kg in both species. Both mice and rats showed clinical signs evocative of health deterioration (decubitus, prostration, decreased activity, weakness, piloerection, soiled urogenital area, nasal discharge); mice had clonic convulsions in the highest dose groups.

- Repeat dose toxicity

Repeat-dose toxicity studies were conducted orally by gavage in mice up to 13 weeks (maximum dose varying from 60 to 500 mg/kg/day), rats up to 6 months (maximum dose varying from 15 to 500 mg/kg/day), dogs up to 3 months (maximum dose varying from 15 to 60 mg/kg/day) and cynomolgus monkey (macaque, *Macaca fascicularis*) up to 1 year (maximum dose varying from 12 to 45 mg/kg/day).

Following rimonabant administration, adverse clinical signs, which varied by species, were observed from 60 mg/kg/day in the mouse (piloerection, hunched posture, lethargy with partially closed eyes, cold to touch, prostration, convulsions), from 6 and 40 mg/kg/day in the female and male rat, respectively (thinness, dried blood on the muzzle, reddening and/or swelling around eyes and red exudates/lacrimation from the eyes, soiled urogenital area, piloerection, dehydration, hypotonia, weakness, loss of balance, prostration, hyperesthesia, hyperexcitability and clonic convulsions), from 1 mg/kg/day in the rabbit (decreased defecation and urination), from 10 to 15 mg/kg/day in the dog (ptyalism from 5 mg/kg/day upwards; tremors, red conjunctiva, ataxia, hypomotility, aggressiveness and startling movements) and from 12 mg/kg/day in the macaque (decreased activity, weakness, somnolence, loss of balance, ataxia, prostration, decubitus, coma, tremors and clonic convulsions). Recovery from the adverse effects (clinical signs, body weight changes and severely decreased food consumption) was generally observed despite continuation of treatment.

Mortality occurred at the highest doses tested and within the first few days or weeks of dosing. In rats, it occurred in males at dose levels ≥120 mg/kg/day or ≥250 mg/kg/day and in females from 60 mg/kg/day. In mice, treatment-related mortality was seen from 120 mg/kg/day. In rabbits, mortality occurred from 5 mg/kg/day. No deaths occurred in the 3-month study conducted in the dog at doses up to 15 mg/kg/day. In the 4-week macaque study, 1 female treated at 45 mg/kg/day was found dead on day 7; the remaining macaques treated at this dose level were euthanized early in the study period due to their poor general health condition. No treatment-related mortality was observed in the 6-month and 1-year chronic studies conducted at dose levels up to 16 mg/kg/day or 12 mg/kg/day.

CNS effects
"Hyperexcitability" was reported in rodents from 30 mg/kg/day: hyperesthesia, tactile hyperesthesia or hypersensitivity to touch, excessive scratching, hyperexcitability, hyperactivity, hypermotility, aggressiveness and combative behaviour. In dogs, at 15 mg/kg/day, aggressiveness and startling movements were noted. Convulsions lasting a few minutes were seen in mice, rats and monkeys. In mice, convulsions were observed from 60 mg/kg/day, in rats from 6 mg/kg/day in females and from 40 mg/kg/day in males, in macaques from 12 mg/kg/day. Rimonabant exhibited a non dose-related

propensity to potentiate pentylenetetrazole-induced tonic convulsions in mice at dose levels ≥10 mg/kg. Thus, rimonabant may have some potential to produce adverse neurological effects; convulsions occurred at systemic exposures below (male rat), similar (female rat) or 2-3 fold (mouse, monkey) human therapeutic systemic exposure.

In CD-1 mice treatment with rimonabant was dose-dependently associated with neuropil vacuolation, most notably in cortical areas, the hippocampus and septal nuclei. This was not observed in rats or cynomolgus monkeys, and in dogs the finding was not clear. In mice, neuropil vacuolation was accompanied by dose-related increased glial fibrillary acidic protein (GFAP) immunoreactivity (i.e. reactive astrocytes indicative of neuronal damage) immunostaining. Applicant was requested by the CHMP to further clarify this issue during the procedure; however, the finding remained unexplained. Yet, the lack of any other signs indicating a neuropathological process in rats, dogs and monkeys, despite a reasonable effort to investigate this, largely diminished the concern regarding the GFAP signal in mice.

Skin abnormalities

An increased incidence of depilated skin areas, variously recorded as hair loss or alopecia, was observed in treated rats. In the one-year cynomolgus monkey study an increased incidence of hair loss was observed in the high dose males.

Bone marrow and haematology

In rats, an increase in the incidence of fatty involution of the bone marrow was observed from 10 mg/kg/day in the 4-week studies. In macaques, "acute changes" described as oedema of the bone marrow were observed in most of the animals given 15 and 45 mg/kg/day. In dogs, a slight increase in the degree of fatty involution was observed at dose levels close to the maximum tolerated dose. No changes were observed in the bone marrow in the 6-month study in rats up to 40 mg/kg/day, 6-month and 1-year studies in macaques up to 16 or 12 mg/kg/day, respectively.

Immunotoxicity

Despite the lack of functional changes in the immune system in a 4-week immunotoxicity study in rats and in the 6-month and 1-year toxicity studies in monkeys, slight haematological changes, including leucopenia and lymphopenia in monkeys were noted in various toxicity studies at clinically relevant doses. At high doses, associated with health deterioration, other effects such as thymus atrophy and decreased spleen weight were also noted.

Liver

An increase in liver weight and size, hypertrophy of centrilobular hepatocytes with ground-glass appearance of the cytoplasm and hyperplasia of the smooth endoplasmic reticulum of hepatocytes at electron microscopy were observed across rodent studies (rats and mice). These types of changes are generally considered to be indicative of liver enzyme induction. Micro- and macrovesicular hepatocyte steatosis was also observed. Focal hepatocellular necrosis occurred slightly more frequently in male rats of the 40 mg/kg dosage group.

Genital tract

In male mice and rats testis, prostate, seminal vesicles and epidydimides were affected, which was probably related to the effects of rimonabant on prolactin and testosterone levels, as discussed under reproductive toxicity below. In female rats, a reversible increase in ovarian (dose-related) and uterine relative weights were observed in females at the end of the 6-month study from 10 mg/kg/day or at 40 mg/kg/day, respectively.

Other hormonal changes

An increase in plasma ACTH concentrations in the six-month rat study at 40 mg/kg/day in females was seen; also relative weight of adrenals and corticosterone serum levels were increased.

- Genotoxicity

The genotoxicity of rimonabant was evaluated in vitro in an Ames test, DNA repair test, and in a gene mutation assay on mouse lymphoma cells, and the clastogenic potential in human lymphocytes and in vivo rat micronucleus test. All of these studies gave negative results with the exception of the first gene mutation assay in mouse lymphoma cells. In that study, a weak increase in mutation frequency and small colonies (reflecting chromosomal aberration) was observed in the presence of metabolic activation at 30 µM. This mutagenic effect was considered as not biologically relevant.

- Carcinogenicity

The oncogenic potential of rimonabant was assessed in mice and rats. No treatment-related proliferative findings were observed in the mouse with doses up to 60 mg/kg/day (maximum tested dose), or in the male rat up to 240 mg/kg/day. In female rat treatment-related neoplastic findings were observed from 20 mg/kg/day (mid-dose group) in the liver (increases in incidences of hepatocellular adenomas) and in the female genital tract (increases in incidence of endometrial polyps and endometrial carcinomas in the uterus and squamous cell carcinomas in the cervix and uterus). The genital tract changes were most likely related to the decreased prolactin levels in these animals. The increased incidences of hepatocellular hypertrophy, foci of cellular alteration and benign liver tumours in rats were considered to be adaptive changes secondary to detoxification and metabolism and excretion of rimonabant. With respect to the occurrence of liver adenomas, there was no safety margin for human therapeutic exposure. Adenomas might have been a consequence of enzyme induction and the subsequent liver hypertrophy as well, and were regarded as rodent-specific. Several other tumour and non-tumour findings supported the probability of a hormonal imbalance.

- Reproduction Toxicity

The effect of rimonabant on fertility and early embryonic development was assessed in male and female rats and in female rabbits. In male rats, fertility was not affected up to 50 mg/kg/day. At higher doses, there was a decrease in the weight of the testis, prostate, seminal vesicles and epididymal fat pad and a decrease in the motility of the spermatozoa. These changes on the male reproduction system were attributed to reversible decreases in testosterone and prolactin concentrations in serum, since both hormones play a major role on spermatogenesis. These changes fully or partially recovered despite continuation of dosing by day 91, and were completely reversed 2 weeks or 4 months after cessation of treatment. In rabbits no adverse effects on the female reproductive system were seen. In female rats (dosing for 2 weeks prior to mating), rimonabant decreased the number of corpora lutea and fertility index, and caused abnormal oestrous cyclicity. The effects on female fertility were attributed to decrease in prolactin concentration in serum due to rimonabant treatment.
In pre/postnatal studies, there was no evidence of rimonabant-induced developmental toxicity at doses up to 20 mg/kg/day in rats and up to 5 mg/kg/day in rabbits. In rats, increases in litter loss were seen at 10 mg/kg/day and an increased number of pups found dead before weaning was seen at maternal doses of 3 and 10 mg/kg/day. In the developmental toxicity studies in rabbits, maternal toxicity was seen at doses 5 and 10mg/kg/day; developmental toxicity was seen at 10 mg/kg/day as decreased litter size, increased post-implantation loss, decreased foetal body weight, and increased malformations (anencephaly, micro-ophthalmia and widened ventricles, omphalocele).

Rimonabant was transferred across the placenta and secreted in milk in rats; it may have inhibited the suckling reflex. Use of rimonabant is contraindicated during lactation (SPC 4.3 and 4.6); it should not be used during pregnancy (SPC 4.6).

- Local tolerance

Rimonabant was not irritating to the skin and eye in the rabbit and was not phototoxic or photoallergic in the guinea pig.

- Other toxicity studies

Dependence
Rimonabant did not display reinforcing properties, but rather interfered with the establishment and maintenance of the reinforcing process of compounds with dependence potential. Besides studies demonstrating precipitation of cannabinoid withdrawal, no specific studies on withdrawal were performed. The absence of appearance of clinical signs in toxicology studies with a recovery period indicated that rimonabant had no potential to produce a withdrawal syndrome.

Ecotoxicity/environmental risk assessment
Rimonabant is poorly soluble in water but is, nevertheless, expected to partition into the organic phase of waste water and migrate to the aquatic part of the environment. Environmental effects testing for rimonabant was performed using established models in algae (*Pseudokirchneriella subcapitata*), zooplankton (*Daphnia magna*), rainbow trout (*Oncorhynchus mykiss*), and activated sludge respiration inhibition. Using the results from most sensitive organism (rainbow trout), a PNEC-value of 0.048 µg/litre was calculated.

Using the forecast estimates by the applicant, the $PEC_{surface\ water}$ was calculated to be 0.026 µg/litre. The applicant was requested to carry out additional studies to further characterise the impact of rimonabant on the environment; these will be done as post-approval follow-up measures.

Discussion on the non-clinical aspects

The pharmacological studies adequately characterised the properties and principal primary and secondary effects of rimonabant, as well as potential harmful effects on essential organ systems. Receptor binding and functional studies in several in vitro and in vivo models demonstrated that rimonabant is a selective CB1 antagonist. Several animal models demonstrated the potential usefulness of rimonabant for the treatment of obesity-related conditions (and nicotine addiction). The safety pharmacology studies identified the CNS and cardiac electrophysiology as possible targets for rimonabant with regard to potential adverse effects in man. Effects on the CNS after a single oral dose comprised sedation and decreased muscle tone. A proconvulsant potential for rimonabant was seen in animals when combined with physical or chemical seizure inducers, or with stressful conditions; this proconvulsant effect was likely to be related to the blockade of an existing endogenous cannabinoid tone. Despite some electrophysiological findings, the non-clinical results raised no concerns that rimonabant could increase the risk of torsade-de-points or other cardiac arrhythmias at therapeutic doses in humans.
The results of the pharmacokinetic studies revealed a consistent picture across the species of the absorption, distribution, metabolism, and excretion of rimonabant: rapid oral absorption, a low to moderate bioavailability, wide distribution (passes the blood-brain barrier and placenta), high protein binding, extensive metabolism (major metabolites are the same in all studied species, including humans), all metabolites observed in humans were present in at least one animal species, long terminal half-life with bile/ faeces being the major excretory pathway, excreted in milk.

One of the major metabolic pathways was hydrolysis of the amide bond that binds the piperidine ring to the rest of the rimonabant molecule, producing the metabolite SR141715, which could, theoretically, release the piperidyl radical as N-aminopiperidine (NAP) in equimolar amounts. This compound is mutagenic in bacteria and may have other genotoxic properties. The applicant calculated that appreciable amounts of NAP was expected to be produced; no additional data about the metabolic fate of NAP was presented. Thus, precise estimate of the risk for humans could not be made but the risk was most likely very low, due to the large exposure margins and absence of tumour findings in the mouse and male rat. The applicant committed to provide additional data on the issue as a post-approval follow-up measure.

The results of the toxicology studies were consistent across species. Reduced weight gain or weight loss and sometimes decreased food consumption were seen at low doses of rimonabant in all species. These findings were likely to be due to a combination of the compound's pharmacological effect and a general health deterioration. At higher doses, detrimental effects on the CNS, with clonic convulsions as a hallmark, was the dominant clinical finding. Particularly in the macaques, this clinical picture was aggravated by fulminant stress reactions that could be lethal. These serious clinical symptoms prompted a reduction of the dose levels in the later studies, especially for the monkeys. There were no apparent signs of a worsening with longer treatment times; on the contrary the clinical symptoms tended to be worst during the first few weeks and declined thereafter. Mortality, generally in conjunction with signs of overall health deterioration, malnutrition and stress, occurred at higher doses (mice and rats ≥ 120 mg/kg/d, macaques ≥ 45 mg/kg/d). In contrast, 'classical' toxicological findings were sparse. There were signs of involvement of the liver, kidneys and bone marrow, but none of these provided clear-cut evidence of a direct toxicity of rimonabant.

The toxic profile of rimonabant was not fully characterized as the highest exposures to rimonabant in the non-clinical safety studies were similar to the expected exposure in humans after the therapeutic dose. The highest doses used in the long-term studies corresponded to about 2-3 times higher exposures in rats and 1.5 times in macaques; testing of higher doses was not feasible. Thus, the non-clinical studies could provide no reassurance regarding margins to the clinical exposure. Consequently, the safe use of rimonabant has to rely more on the clinical safety data and on the post-approval pharmacovigilance programme.

No signs of genotoxicity were observed in a standard in vitro package or in a mouse micronucleus test. However, the applicant committed to further clarify the bioactivation of N-aminopiperidine.

The tumour findings in the liver and female genital tract found in the long term rat study were considered to be species specific and due to enzyme induction and chronic hormonal imbalance with oestrogen stimulation, respectively. Consequently, these tumours should not imply an increased risk for humans.

The most remarkable effects in the reproductive toxicity package were decreased viability index and pup growth pre-weaning, in conjunction with an increased incidence of no milk in the stomach; the mechanism(s) of these effects was not clear, but could be related to an effect on the suckling reflex. There were malformations in the rabbit embryo-foetal development studies (omphalocele and various CNS-malformations) that could be due to rimonabant. Moreover, it is known that CB1 is expressed in many parts of the developing brain and that the pattern changes during development. These findings resulted in a warning against the use of rimonabant during pregnancy and in a contraindication during lactation (SPC 4.3 and 4.6).

The finding of neuropil vacuolation and increased GFAP staining in rimonabant treated mice, which could be a signal of underlying neuropathology, was diminished by the lack of other signs.

Finally, the environmental impact of rimonabant needed further evaluation and additional studies; the applicant committed to carry out such studies as a post-approval follow-up measure.

4. Clinical aspects

Introduction

The Clinical trials were performed in accordance with GCP as claimed by the applicant. Further, at the request of the CHMP, a GCP-inspection was carried out at two of the 60 investigational sites of study "RIO-Europe" (at one investigator's site in Netherlands and one in Sweden). The results of the inspection

of both investigator sites demonstrated, that the data produced by these sites were verifiable and reliable and in line with the data reported to the CHMP.

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.

Pharmacokinetics

The Phase 1 clinical pharmacology program included 36 studies. In addition, two population PK analyses were performed using sparse data from a large number of patients included in the phase III studies. Rimonabant plasma concentration was determined by a LC/MS/MS methods in main PK studies. Pharmacokinetic parameters were determined using non-compartmental models. Population pharmacokinetics analyses were conducted using WinNonmix and NONMEM.

- Absorption

Rimonabant was rapidly absorbed upon oral administration. The absorption rate was dose dependent and decreased with increased dose. Peak plasma concentration (C_{max}) was reached about 2 hours after administration of a 20 mg dose. The absolute bioavailability was not determined. Rimonabant had low solubility and high permeability. Rimonabant was not a substrate or inhibitor of P-gp. The pharmacokinetics were roughly dose proportional up to about 20 mg, the exposure thereafter increased less than in proportion to dose. During concomitant food intake C_{max} increased by about 70% and AUC by 50%; the SPC recommends intake with breakfast in line with the conducted phase III studies. Steady state was reached after a median time of 13 days in healthy normal-weight volunteers. In obese patients median time to steady state was estimated to be 39 days, as a consequence of their higher volume of distribution and longer half-life.

Bioequivalence between the 20 mg tablet applied for and the capsule formulation used during clinical development was demonstrated.

- Distribution

Rimonabant has not been administered intravenously to humans, and V_{ss} was not determined. Data on V/F suggest extensive distribution. Rimonabant exhibited very high binding to plasma proteins (mean = 99.94%), mainly albumin. Due to the large volume of distribution, little impact was expected on interaction caused by protein displacement, in spite of the high protein binding of rimonabant.

- Elimination

Rimonabant is mainly eliminated by metabolism and subsequent biliary excretion of metabolites. The mean terminal half-life of rimonabant was about 10 days in healthy (normal weight) subjects but was higher in obese subjects (16 days). The clearance (Cl/F) was approximately 5 L/h. Approximately 32% of administered rimonabant was excreted as unchanged drug in faeces, probably representing unabsorbed drug. No unchanged rimonabant was found in urine. Approximately 3% of a 20 mg rimonabant dose was excreted in urine and about 61% of the dose was eliminated in faeces over 312 hours. When extrapolated to infinity about 90% of the total administered dose could be accounted for (86 % and 4% in faeces and urine, respectively). *In vitro* data indicated that rimonabant was metabolized by CYP3A4 and in lesser extent amidohydrolase (predominantly hepatic) pathways with the fraction metabolized varying between 25% to 63%. The following metabolites of rimonabant were identified in humans: SR141715 (carboxylic acid derivative of rimonabant), SR142923 (hydroxy derivative on the piperidine ring), SR90161 (propionic acid derivative of SR142923), glucuronidated SR141715 (H3) and SR90161, hydroxy unsaturated or lactam derivative of rimonabant. The metabolites identified in plasma (SR141715, SR142923, and SR90161, representing 11%, 5%, and 8% of total plasma radioactivity, respectively) were inactive against human cloned CB1 receptors. No consequences of genetic polymorphism were expected, as rimonabant was not metabolized by CYP2D6, CYP2C9 or CYP2C19 isoenzymes.

- Variability

Inter-individual variability in CL/F was 44-46% in the population PK studies. Residual variability (representing intra-individual variability) was 24% in POH0045. In crossover studies in healthy subjects, the inter-individual variability was 41% for C_{max} and 53% for AUC and the within-subject variability was 29% for C_{max} and 17% for AUC.

- Special populations

Two large population pharmacokinetic analyses and specific phase I studies were conducted evaluating the effect of age, gender, race, body size (body weight, body mass index, height), hepatic function, renal function and dose on rimonabant pharmacokinetics (PK).

The main factor influencing rimonabant exposure was race with Afro-Americans having higher clearance and hence lower exposure than Caucasians (43% lower AUC); this is reflected in SPC (5.2). Volume of distribution increases with weight resulting in longer half-life and subsequently longer time to steady state and lower fluctuations at steady state. Race, other than Afro-Americans or gender had no clinically relevant influence on rimonabant PK. AUC was estimated to be 27% higher in a 75 year old than in a 44 year old. However, this difference is of limited clinical relevance. There were no data in children or adolescents. The population pharmacokinetic analyses indicated that rimonabant pharmacokinetics were similar between healthy non-smoking subjects, patients who smoke, and obese patients. The applicant committed to provide additional safety data on other ethnic groups than Afro-Americans (in Japanese and Asiatic patients) as a post-approval follow-up measure.

The influence of renal function on the PK of rimonabant was not evaluated in a specific study. Based on data from phase III studies, AUC was estimated to be 40% higher in patients with moderate renal impairment than in patients with normal renal function. Data were too sparse to draw conclusions in patients with severe renal impairment. Rimonabant should be used with caution in patients with moderate renal impairment and use is not recommended in patients with severe renal impairment (see SPC 4.4). The applicant committed to study PK in patients with severe renal impairment as a post-approval follow-up measure.

A specific study was conducted in subjects with mild and moderate hepatic impairment. There was no significant difference in total or unbound AUC between subjects with impaired hepatic function and control subjects. A prolongation of half-life was observed, caused by an increased volume of distribution. There were no data in severe hepatic impairment. Rimonabant should be used with caution in moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment (see SPC 4.4).

- Pharmacokinetic interaction studies

In vitro

The in vitro studies suggested a low potential for inhibition or induction of CYP450 isoenzymes by rimonabant. It had mild inhibitory effect on CYP2C8.

In vivo

No effect of rimonabant (40 mg o.d. for 8 days) on the pharmacokinetics of the CYP3A4 substrate midazolam (0.03 mg/kg single oral dose) was observed in study INT5006. No effect of rimonabant (40 mg o.d. for 8 days and 6 days continued after warfarin administration) on the pharmacokinetics of warfarin (30 mg single dose), a narrow therapeutic index drug and a CYP2C9 substrate, was observed in study INT3787. No effect of rimonabant (40 mg o.d. for 8 days) on the pharmacokinetics of digoxin (0.50 mg loading dose + 0.25 mg once-daily), a narrow therapeutic index drug and a P-gp substrate was observed in study INT3786. Study INT4478 showed that rimonabant (40 mg o.d. for 8 days) did not affect the pharmacokinetics of nicotine (21 mg once-daily). Study INT4738 showed that rimonabant (40 mg o.d. for 8 days) did not affect the pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol + 0.15 mg

levonorgestrel once-daily).

Seven days of treatment with a daily oral dose of 200 mg ketoconazole increased C_{max}, AUC_{0-24h}, and AUC_{inf} of rimonabant by 1.42 (90% C.I.: 1.18, 1.70), 1.55 (90% C.I.: 1.43, 1.68), and 2.04 (90% C.I.: 1.89, 2.23)-fold, respectively (study INT3785). A small but statistically significant difference between the $t_{1/2}$ values of rimonabant with and without ketoconazole treatment was observed. No differences were observed for the t_{max} after both treatments. Thus, caution is advised during combined treatment with potent CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin and nefazodone). (See SPC 4.5).

In study INT3802 coadministration of 120 mg TID for 6 days of orlistat, a drug used in the management of obesity but no substrate or inhibitor of CYP enzymes, had a significant, but small, effect on mean C_{max} (0.72-fold) of rimonabant (40 mg). None of the other pharmacokinetic parameters were affected.

Coadministration of 500 mg TID of famciclovir, an antiviral drug, had no effect on the pharmacokinetics of rimonabant (40 mg) (study INT5501). Famciclovir is metabolized in the liver, but the P450 cytochrome system is not involved.

Pharmacodynamics

- Mechanism of action

Rimonabant is a selective antagonist of the cannabinoid type 1 (CB1) receptors in the CNS.

At the level of the CNS, and in particular the mesolimbic system, the majority of data with regard to the cannabinoid receptors is derived from the therapeutic and recreational use of its primary ligand, cannabis. Cannabis induces psychotic features and psychosis at chronic use, and may even facilitate the first onset of schizophrenia[1]. Cannabis may induce anxiety and depression[2], and cognitive impairment, especially of attention and memory[3]. On the contrary, decrease in the availability of dopamine in the CNS may cause depression, and is one of the basic principles behind the use of antidepressants. Rimonabant indirectly decreases dopamine release in different brain areas by blocking the CB1 receptor.
The mode of action of rimonabant with regard to obesity is interference with feelings of hunger and satiety in the hypothalamic region. In addition it has effect on the peripheral adipocytes. The applicant suggested that in smoking cessation its mode of action is based on antagonism of CB1 receptors expressed in the mesolimbic dopamine system, a brain circuit that is involved in addictive behaviour; rimonabant would antagonize nicotine-seeking behaviour in animals, through blockade of dopamine release in this area, which is also referred to as the CNS reward system[4].

- Primary and Secondary pharmacology

The pharmacodynamics of rimonabant was investigated in numerous separate studies (s*ome examples are reported below).*

Study in obesity
The effects of 7-day repeated doses of 20 mg rimonabant on hunger, satiation, satiety, and food consumption, compared with placebo, to explore the effect of rimonabant on hedonic ratings of sucrose

[1] Maki P et al. Predictors of schizophrenia-a review. Br Med Bull 2005; 73: 1-15.
[2] Raphael B et al. Comorbidity: cannabis and complexity. J Psychiatr Pract 2005; 11 (3): 161-176)
[3] Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol Biochem Behav 2005; 81: 319-330.
[4] Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry 2004; 12: 305-320.

alone and in food vehicle, and the effects of rimonabant on food consumption were studied. Visual Analoque Scale (VAS) scores for hunger, recorded before self-selected meals, and cumulated over one week, were statistically significantly reduced with rimonabant when compared with placebo (p=0.0355). The daily caloric intake was consistently lower (although not statistically significant) with rimonabant compared with placebo. A reduction in subjects' mean body weight was observed following 7-day treatment with rimonabant (-620 g); the difference versus placebo (-720 g) was statistically significant (p=0.008). There was no treatment effect observed on eating disorder inventory or Beck depression score.

Antagonism of cannabis effects
In a study the 90 mg dose of rimonabant produced inhibition of cannabis-induced effects, being statistically significant for VAS composite score. In a second study, rimonabant at both doses (90 mg single doses, 40 mg repeated doses) inhibited cannabis induced heart rate increase. The results suggested that rimonabant could attenuate the effects of smoked cannabis; since rimonabant did not affect the pharmacokinetics of cannabis, this effect was considered to be due to its antagonistic effects on CB1 receptors.

Effects on cognitive functions

The impact of rimonabant on cognitive function was assessed in various clinical pharmacology studies. The overall analysis of this large database lead to the conclusion that rimonabant is devoid of any significant effect on cognitive abilities, and in particular does not show any sedative or stimulant properties, even at high doses (300 mg single doses, 60 mg 21-day repeated doses)

Electrophysiological effects
Results from studies investigating effects on EEG showed that there were unspecific changes showing that rimonabant crossed the blood-brain barrier.

The effect on ECG parameters of rimonabant 20 mg and 60 mg compared to placebo and with moxifloxacin 400 mg as a positive control was studied. There was no evidence that rimonabant prolonged ventricular repolarisation. There was no significant relationship between the QT changes from baseline as measured by the Holter method or from extracted ECGs and rimonabant plasma concentrations.

PK/PD
A relationship between weight decrease and concentration was shown. The variability in weight reduction was very large. The relationship between exposure and weight reduction was analysed in different PK/PD models. With a Hill model, E_{max} was estimated to be about 6.5 kg and AUC_{50} 1530 ng·h/ml. With the exposure obtained with 20 mg q.d. (AUC 3800 ng·h/ml) a large part of the patients were at the flat part of the concentration response curve supporting the chosen dose.

Clinical efficacy

The clinical dossier comprised of two parts, one concerning obesity and related disorders (Obesity program), and one concerning smoking cessation. These will be discussed separately.

OBESITY
In support of the efficacy of rimonabant in the treatment of obesity and related disorders six studies were submitted: 1 dose-ranging study (DRI3388; based on the results of this study the 5 mg and 20 mg doses were selected for Phase III studies); 1 study investigating the effect of 40 mg of rimonabant versus placebo on energy expenditure and food intake (PDY3796); 4 adequate and well-controlled Phase III studies, RIO-North America (EFC4743), RIO-Europe (EFC4733), RIO-Lipids (EFC4735), and RIO-Diabetes (EFC4736) were conducted to demonstrate the efficacy and safety of 2 doses of rimonabant 5

mg and 20 mg versus placebo. This clinical development program was designed in accordance with the clinical development guidelines of drugs in obesity, both in Europe and in the USA.

- Dose response studies

The PDY3796 study was as a double-blind, parallel group, placebo-controlled exploratory study of the effects of 4-week of rimonabant 40 mg daily on energy expenditure (primary endpoint) and food consumption in 45 obese volunteers. The patients were not on a restrictive diet, and the pharmacodynamic activity of rimonabant was assessed primarily by measuring total energy expenditure in a calorimetric chamber. Energy intake was measured at baseline and endpoint in buffet sessions and the amount of food consumed by the patients who were offered a cold buffet-like meal at noon. Compared with placebo, 40 mg rimonabant reduced the mean total energy intake and the mean energy intake from carbohydrate and fat. Body weight decreased by –4.3 ± 1.8 kg in the 40 mg group versus –1.7 ± 1.7 kg in the placebo group at week 6 follow-up visit. No significant difference in energy expenditure was seen between the treatment groups.

The DRI3388 study was the principal clinical dose ranging study in treatment of obesity and was performed as a double-blind, placebo-controlled study evaluating the efficacy and safety of 3 doses of rimonabant in 287 obese patients (30 kg/m^2≤BMI≤40 kg/m^2) over 16 weeks. Patients were randomly allocated to 5, 10 or 20 mg/day of rimonabant or placebo after a 2-week single-blind placebo run-in period and a modest hypocaloric (-500 kcal/day) diet. The primary efficacy outcome was assessed by the mean change in body weight in both the intention-to-treat (ITT; 265 patients) and efficacy evaluable (EE) (175 patients) populations. The ITT corresponded to all patients who were randomised and took at least 1 dose of study medication: The EE population excluded ITT patients who had 1 or more major protocol violations and those who failed to complete their prescribed dosing. A significant treatment effect of all doses of rimonabant was observed with 20-34% of patients on rimonabant losing ≥5% of their baseline body weight, compared with 7% in the placebo group (p = 0.0395 for 5 mg, 0.0045 for 10 mg, and p = 0.0001 for 20 mg, respectively); see Table 1 below.

Table 1: Study DRI3388, weight reduction after 16 weeks of treatment, (rimonabant=SR)

		Placebo N, mean, (SD)	SR 5 mg N, mean, (SD)	SR 10 mg N, mean, (SD)	SR 20 mg N, mean, (SD)
Mean Change (kg)	Week 16, EE pop	40, -1.1 (2.7)	45, -3.4 (4.2)	39, -3.7 (3.4)	51, -4.5 (3.6)
	LOCF, ITT	70, -0.5 (3.7)	61, -2.5 (4.2)	66, -2.7 (3.3)	68, -3.8 (3.7)
Percent change	Week 16, EE pop	40, -1.2 (2.8)	45, -3.6 (4.2)	39, -4.0 (3.5)	51, -4.8 (4.1)
	LOCF, ITT	70, -0.6 (3.5)	61, -2.6 (4.3)	66, -2.8 (3.3)	68, -4.0 (4.1)

- Main studies

METHODS
Four phase III clinical trials were conducted in the treatment of obesity and obesity-related metabolic disorders. (See Table 2 below.)

The studies were double-blind, placebo-controlled with 3 parallel treatment groups (20 mg or 5 mg of rimonabant or placebo); they had the same primary endpoint and similar secondary endpoints (adapted to the specific population recruited in a given study and the tests performed); the same inclusion and exclusion criteria were used (except for those to define specific populations); the scheduled visits were planned at the same time points.

Study participants, treatments

Table 2: Summary of the four main studies in the obesity-related indications

Study	Number of study centers	Treatment arms	Number of patients entered/ completed	Treatment Duration	Diagnosis, Inclusion criteria
EFC4743 RIO-North America Year 1	72 USA, Canada	Rimonabant 5 mg Rimonabant 20 mg Placebo	1214/620 1219/673 607/309	52 weeks	BMI ≥30 kg/m² or BMI>27 kg/m² with hypertension[a] and/or dyslipidaemia[b]. Stable body weight. Dietary restrictions. Type 2 diabetes excluded.
Year 2 Re-randomisation of active treatment groups to same dose or placebo		Rimonabant 5 mg/Placebo Rimonabant 5/5 mg Rimonabant20mg/Placebo Rimonabant 20/20 mg Placebo/Placebo	300/210 300/215 326/225 333/257 298/214	52 weeks	Patients from Year 1 who achieved 1 year of treatment.
EFC4733 RIO-Europe	60 Belgium, Finland, France, Germany, Netherlands Sweden, USA	Rimonabant 5 mg Rimonabant 20 mg Placebo	603/379/288 599/363/268 305/178/128	104 weeks	BMI ≥30 kg/m² or BMI>27 kg/m² with hypertension[a] and/or dyslipidaemia[b.] Stable body weight. Dietary restrictions. Type 2 diabetes excluded.
EFC4735 RIO-Lipids	67 Australia Finland, Italy, Spain, Sweden, Switzerland Canada, USA	Rimonabant 5 mg Rimonabant 20 mg Placebo	345/208 346/221 342/214	52 weeks	BMI >27 kg/m² and ≤40 kg/m². Untreated Dyslipidaemia[c]. Stable body weight. Dietary restrictions. Type 2 diabetes excluded.
EFC4736 RIO-Diabetes	159 Belgium, Czech Rep., France, Poland, Germany, Netherlands Finland, UK, USA, Canada Argentina	Rimonabant 5 mg Rimonabant 20 mg Placebo	358/232 339/229 348/231	52 weeks	BMI >27 kg/m² and ≤40 kg/m². Treated type 2 Diabetes[d]. Stable body weight. Dietary restrictions.

[a]drug-treated for hypertension and/or BP ≥ 140 and/or 90 mmHg

[b]drug-treated for dyslipidaemia and/orLDL-cholesterol ≥ 3.36 mmol/L and/or HDL-cholesterol <1.03 mmol/L and/or triglyceridemia ≥1.69 mmol/L

[c]low HDL-C defined by the total-C/HDL-C ratio >4.5 in women or >5 in men and/or elevated TG (TG >1.69 mmol/L), and who were not receiving drug treatment for their abnormal lipid profile.

[d]treatment with biguanides **or** sulfonylureas

The main exclusion criteria were standard for phase III studies, i.e. any severe medical condition that would interfere with the participation of the patient in long-term studies (including presence of any clinically significant cardiovascular or pulmonary disease according to the investigator, history of stroke within six months prior to screening visit, presence of treated epilepsy, presence of any clinically significant hepatic or gastrointestinal disease according to the investigator, creatininemia > 150 µmol/L), concomitant drugs that would have any impact on body weight, patients with DSM-IV defined eating disorders, patients with a history of severe depression.

Outcomes and endpoints
The primary and secondary efficacy parameters are summarised in Table 3 below.

Table 3: Summary of primary and secondary efficacy parameters, main studies

Efficacy parameters	EFC4743 RIO-North America	EFC4733 RIO-Europe	EFC4735 RIO-Lipids	EFC4736 RIO-Diabetes
Primary	Weight loss and weight maintenance over a period of one year Prevention of weight regain during a second year of treatment in obese patients with or without comorbidities	Weight loss and weight maintenance over a period of one year.	Weight loss and weight maintenance over a period of one year.	Weight loss and weight maintenance over a period of one year.
Secondary	The effect over a period of 2 years on: -Weight maintenance -Hypertension -Dyslipidaemia -Quality of life -Safety and tolerability -Withdrawal-emergent disorders in obese patients who are re-randomized to placebo after one year of treatment.	The effect over a period of 2 years on: -Weight loss and weight maintenance –Hypertension –Dyslipidaemia -Glucose tolerance status (OGTT): rate of deterioration of glucose tolerance status, rate of improvement of glucose tolerance status -Fasting blood glucose and insulin -Quality of life, satisfaction, food behaviour -Food intake and compliance to dietary prescription.	The effect over a period of 1 year on: -Dyslipidaemia (triglycerides, HDL-C, LDL-C, small dense LDL particles and other lipid parameters) -Hypertension, -Glucose tolerance status (OGTT): rate of progression to the development of impaired glucose tolerance and type 2 diabetes, rate of improvement of glucose tolerance status. -Fasting glycemia and insulinemia -Quality of life, satisfaction, hunger scale. -Food intake and compliance to dietary prescription.	The effect over a period of 1 year on: -Glycemic control -Hypertension -Dyslipidaemia -Quality of life -The safety and tolerability

In the CHMP guideline on drugs used in weight control a weight loss of 10 % is considered to be a valid primary efficacy criterion. Such responder analyses were included as secondary efficacy parameters in the RIO-programme. Sleep apnoea episodes were not recorded.

The prevalence of metabolic syndrome was analysed in the pooled population from the four studies. The criteria recommended by the National Cholesterol Education Program- Adult Treatment Panel III (NCEP-ATPIII) were used (ie, waist circumference >88 cm in females or >102 cm in males, HDL-C<1.295 mmol/L in females or <1.036 mmol/L in males, TG≥1.69 mmol/L, systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, fasting glucose ≥6.11 mmol/L) and the percentages of patients having at least 3 out of the 5 criteria of the metabolic syndrome at endpoint were compared.

Objectives
Objective of all 4 studies was to establish the long-term efficacy and safety of rimonabant in the treatment of obesity and obesity-related metabolic disorders.

Sample size
In order to have sufficient power to detect a statistical significant difference between placebo and rimonabant, the total number of subjects needed was 1400 subjects in RIO-Europe (difference in weight loss between rimonabant and placebo after one year 3 kg, SD= 10 kg, $\alpha = 0.025$, power = 0.96, 30% drop-out rate), 990 subjects in RIO-Lipids and RIO-Diabetes (difference in weight loss between rimonabant placebo after one year 3 kg, SD= 10 kg, $\alpha = 0.025$, power = 0.96, 30% drop-out rate), and 2800 subjects in RIO-North-America (first year analysis: 560 subjects in the placebo arm and 1120 subjects in the rimonabant arms; difference in weight after one year between rimonabant and placebo 3 kg, SD = 10 kg, two-sided $\alpha = 0.025$, power = 0.99, 34% drop-out rate; second year analysis 740 subjects in each re-randomised arm; difference in weight gain after 2 years 2.5 kg, SD = 10 kg, two-sided $\alpha = 0.025$, power = 0.88).

Randomisation, Blinding (masking)
After a 4-week run-in period on diet, subjects compliant to dietary instruction and treatment were randomised to placebo, rimonabant 5 mg or rimonabant 20 mg. Blinding was ensured by identical capsules and standard operational procedures. Duration of the double-blind period was 1 or 2 years. In RIO-North-America subjects were re-randomised after one year.

Randomisation was performed centrally. In RIO-North-America and RIO-Europe randomisation ratio was 1:2:2 for the placebo, 5 mg and 20 mg arm respectively. In RIO-/Lipids/Diabetes the randomisation ratio was 1:1:1. Randomisation was stratified by degree of weight loss in the screening phase on diet alone (less that 2 kg weight loss versus more than 2 kg weight loss). Additional stratification factors were TG-status (≤ 4.0 g/l versus >4.0 g/l) in RIO-Lipids and anti-diabetic treatment (biguanides vs. sulfonylureas) in RIO-Diabetes.

In RIO-North-America subjects in the rimonabant arms were re-randomised to placebo or to the same dose of rimonabant after one year. Patients initially randomised in the placebo group remained on placebo. After re-randomisation there were 5 groups with an equal number of patients: $\text{placebo}_{\text{year 1}}$-$\text{placebo}_{\text{year 2}}$, 5 mg $\text{rimonabant}_{\text{year 1}}$-$\text{placebo}_{\text{year 2}}$, 5 mg $\text{rimonabant}_{\text{year 1}}$-5 mg $\text{rimonabant}_{\text{year 2}}$, 20 mg $\text{rimonabant}_{\text{year 1}}$-$\text{placebo}_{\text{year 2}}$ and 20 mg $\text{rimonabant}_{\text{year 1}}$-20 mg $\text{rimonabant}_{\text{year 2}}$. Weight change between 1-2 years was to be used to support the claim of reduction in weight regain after prior weight loss.

Statistical methods
The primary analysis dataset was the intention-to-treat (ITT) population defined as all randomised subjects who received at least one dose of double-blind study drug, had at least one post-baseline assessment and a baseline assessment. For RIO-North-America the ITT-population was defined for 3 periods i.e. the one-year intent-to-treat population (ITT1), the year two intent-to-treat population

including the subjects re-randomised for the efficacy analysis in week 52 through 104 (ITT2) and the intent-to-treat population for the whole two year study period (week 0-104). A last observation carried forward procedure was followed for post baseline missing values.

For the primary endpoint, weight loss at one year, an ANOVA was performed with treatment and randomisation strata as fixed effects. Prevention of weight regain during the second year, the other primary endpoint of RIO-North-America, was analysed by ANCOVA with treatment after re-randomisation, randomisation strata as fixed effects. Each re-randomised group was compared to their corresponding placebo group. For the secondary endpoints an ANOVA was used for continuous variables and a Chi-square or Fisher's exact test for categorical secondary variables.

Table 4: Endpoints / analysis / subgroups

	RIO-North-America	**RIO-Europe**	**RIO-Lipids**	**RIO-Diabetes**
Confirmative end points				
Primary	Body weight at 1 y Body weight regain at 2 y	Body weight at 1 y	Body weight at 1 y	Body weight at 1y
Secondary	% change in HDL-C % with metabolic syndrome	% change in HDL-C % change in TG % with improved OGTT at 1 year % with metabolic syndrome	% change in HDL-C % change in TG % with improved OGTT % with metabolic syndrome	Absolute change in HbA_{1c} % change in HDL-C % change in TG % with metabolic syndrome
Supportive endpoints	At 2 years: Weight loss / - maintenance / Metabolic syndrome at 2 years	At 2 years: Weight loss / -maintenance / OGTT / Improved OGTT / Metabolic syndrome	TG by baseline TG levels HDL-cholesterol by baseline HDL-cholesterol levels OGTT at 1 year	Reduction in anti-diabetic medication
	Waist circumference; Triglycerides, Total cholesterol/HDL-cholesterol ratio, Fasting glucose, Fasting insulin, OGTT			

The confirmatory secondary endpoints were intended "to be used as part of a formal decision making process to determine a regulatory claim". A hierarchical testing strategy was implemented in each study to ensure a global type 1 error rate of 5%. If significance was reached for weight loss at 1 year then the next confirmatory endpoint was to be tested for the corresponding dose at a 5% level. If both doses reached significance for weight loss at 1 year the modified Bonferroni procedure (Hochberg) was to be applied for that endpoint.

To evaluate the relationship between weight loss and secondary endpoints an analysis of covariance was performed for continuous parameters and a logistic regression model for categorical parameters. The model included weight loss as an additional covariate.

For the intent-to-treat population, weight loss at one year and weight re-gain were examined using a number of covariates (including age, gender, race, BMI, smoking status, education status, socio-economic status, concomitant medications, waist circumference, history of diabetes, history of hypertension, history of dyslipidaemia, caloric intake at baseline) to examine their potential effects. To investigate the relationship between treatment and covariate, each factor was analysed statistically using a two-way analysis of variance model with terms for treatment, the covariate, and the treatment by covariate interaction.

RESULTS

Baseline data
Table 5 below describes some baseline characteristics of the study populations.

Table 5: Some baseline characteristics of the obesity study populations

		RIO-North America (N=3040)	RIO-Europe (N=1507)	RIO-Lipids (N=1033)	RIO-Diabetes (N=1045)
Age (years)	N	3040	1507	1033	1045
Mean (SD)		45.0 (11.6)	45.0 (11.5)	47.8 (10.1)	55.6 (8.6)
Gender	Males	19.3%	20.5%	39.4%	49.1%
	Females	80.7%	79.5%	60.6%	50.9%
Weight (kg)	N	3039	1507	1033	1045
Mean (SD)		104.4 (21.3)	101.0 (19.8)	94.1 (14.8)	96.3 (14.7)
Waist (cm)	N	3032	1504	1033	1044
Mean (SD)		105.8 (15.3)	108.4 (14.1)	105.0 (11.1)	109.0 (10.8)
	Males >102cm	527 (89.6 %)	289 (93.5 %)	320 (78.6 %)	416 (81.3 %)
	Females >88cm	2124 (86.9 %)	1132 (94.7 %)	571 (91.2 %)	514 (96.6 %)

Approximately 55-60% of the included patients had dyslipidaemia at baseline in the different studies (100% in the RIO-lipids). Prevalence of hypertension was between 27 and 61 % with the highest prevalence in the RIO-diabetes study; the number of patients treated for hypertension varied from 55% in RIO-Europe to 93% in RIO diabetes and was approximately 68% in the RIO-North America and RIO-Lipids studies. Mean BMI varied between 33.3 and 37.6 kg/m^2. Forty-six per-cents of the patients were either current or former smokers.

Overall, 46.5% of the patients included in the RIO studies had metabolic syndrome with prevalences of 35, 41, 54 and 79% in the RIO-North America, RIO-Europe, RIO-Lipids and RIO-Diabetes, respectively.

No imbalances between treatment groups within the studies with regard to demographics, BMI or co-morbidities were seen. The low proportion of men in the RIO-Europe and RIO North America was noted. Elderly patients (>75 years of age) were poorly represented, which is reflected in the SPC (4.4).

Overall, the percentages of patients who completed 1 year of treatment were 52.5% in RIO-North America, 60.8% in RIO-Europe, 62.1% in RIO-Lipids and 66.1% in RIO-Diabetes. The total dropout rates were rather similar in the different treatment groups but generally higher due to adverse events in the 20 mg group and higher due to patients' request in the placebo and 5 mg groups.
The high withdrawal rates were noted but not unexpected in this kind of studies and they are essentially similar to those observed in earlier similar trials with weight reducing agents.

Outcomes and estimation

Body weight and related endpoints
The effect of rimonabant 20 mg on body weight was similar in the 3 RIO studies including non-diabetic patients. A mean body weight loss of 6.3 to 6.9 kg from baseline was observed at 1 year in the ITT population (LOCF). The weight reduction in the placebo groups was similar across these 3 studies with body weight loss of 1.5 to 1.8 kg. The mean body weight loss difference of the 20 mg dose over placebo ranged from 4.7 kg in RIO-North America and RIO-Europe to 5.4 kg in RIO-Lipids ($p<0.001$). In RIO-Diabetes the body weight loss from baseline was slightly lower in both groups, rimonabant 20 mg (-5.3 kg) and placebo (-1.4 kg), but with a significant difference between the 2 groups (-3.9 kg, $p<0.001$). (See Table 6.)

The effects demonstrated by the 5 mg dose were consistently lower than the effect of the 20 mg dose with a mean difference of –1.4 kg (p<0.01) and -0.8 kg (p=0.013) vs. placebo in non-diabetic and diabetic patients, respectively.

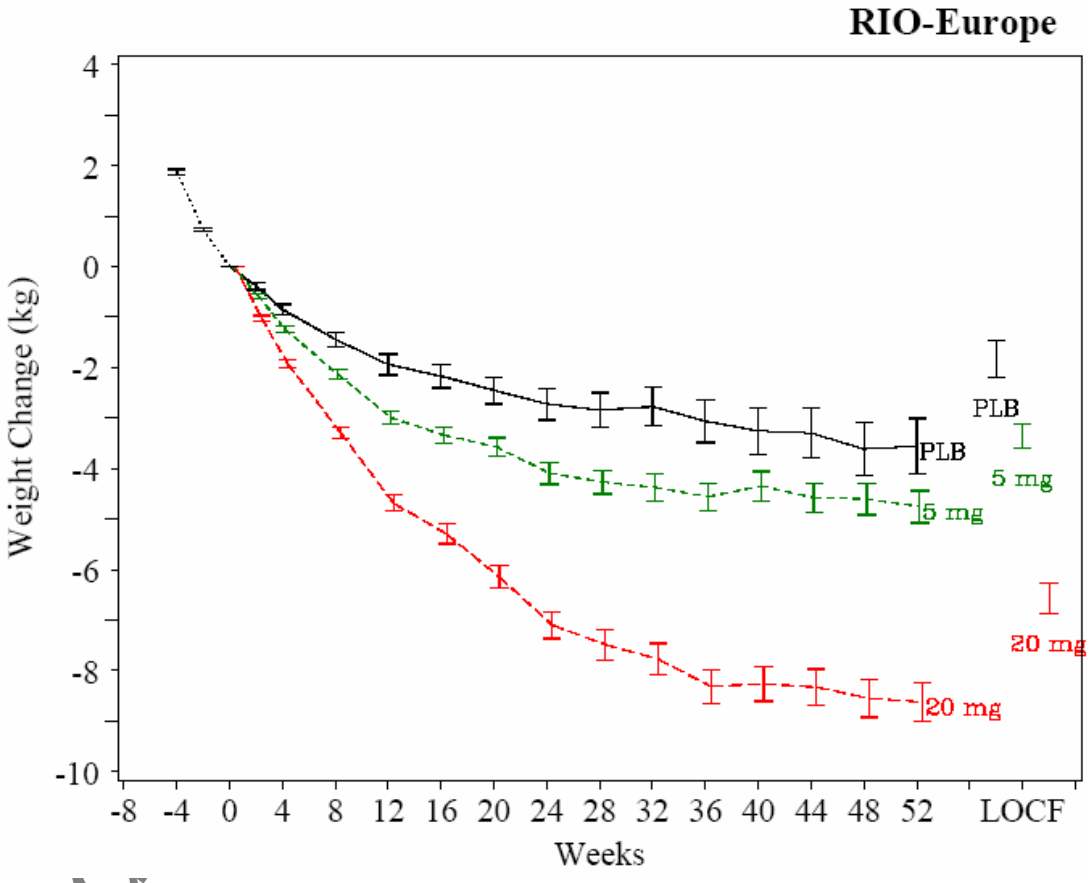
Table 6: Body weight results in the four pivotal studies, change in kg from baseline and responder rates

		RIO-North America		RIO-Europe		RIO-Lipids		RIO-Diabetes	
		Placebo (N=607)	20 mg (N=1219)	Placebo (N=305)	20 mg (N=599)	Placebo (N=342)	20 mg (N=346)	Placebo (N=348)	20 mg (N=339)
Baseline	N Mean (SD)	590 104.7 (21.7)	1189 103.0 (20.3)	302 99.9 (20.2)	595 101.7 (19.4)	334 95.0 (15.1)	344 93.4 (14.8)	345 96.0 (15.1)	336 95.7 (14.2)
Year 1	Mean (SD)	103.1 (22.6)	96.7 (21.0)	98.1 (20.9)	95.1 (20.6)	93.5 (15.9)	86.4 (15.4)	94.5 (15.2)	90.3 (14.5)
Change	Mean (SD) LS mean difference (SE) [95% CI] p vs placebo	-1.6 (5.7)	-6.3 (7.1) -4.7 (0.3) [-5.4,-4.1] <0.001	-1.8 (6.4)	-6.6 (7.2) -4.7 (0.4) [-5.6,-3.8] <0.001	-1.5 (5.0)	-6.9 (6.1) -5.4 (0.4) [-6.2,-4.6] <0.001	-1.4 (3.6)	-5.3 (5.2) -3.9 (0.3) [-4.6,-3.3] <0.001
% Change	Mean (SD)	-1.6 (5.4)	-6.2 (6.9)	-1.8 (5.9)	-6.6 (7.2)	-1.6 (5.2)	-7.5 (6.4)	-1.5 (3.6)	-5.6 (5.4)
5% responder	n (%) p vs placebo	118 (20.0)	578 (48.6) <0.001	58 (19.2)	303 (50.9) <0.001	65 (19.5)	201 (58.4) <0.001	50 (14.5)	166 (49.4) <0.001
10% responder	n (%) p vs placebo	50 (8.5)	300 (25.2) <0.001	22 (7.3)	163 (27.4) <0.001	24 (7.2)	112 (32.6) <0.001	7 (2.0)	55 (16.4) <0.001

The ITT analyses were supported by the analyses performed on patients completing treatment where weight reduction generally appeared somewhat more pronounced.

The weight effects over time were very similar in the four studies and are presented in Figure 1 below with the RIO-Europe results. The weight reduction reached a plateau after approximately 36 weeks.

Figure 1: Weight reduction over time in the RIO-Europe study



The decrease in the waist circumference in the rimonabant treated patients paralleled the decrease in body weight with mean decreases (relative to placebo) varying between 3.3 and 4.7 cm (p<0.001 in all studies) with absolute decreases from baseline between 5.2 and 7.1 cm.

Body composition was measured in a subgroup of patients and a decrease in the total body fat mass was demonstrated in the 20 mg group.

The effects on body weight and related criteria appeared to be consistent among men and women (mean weight reductions 5.1 and 4.8 kg, respectively), in different geographic regions, in different age groups and among smokers/non-smokers.

The effects also appeared essentially consistent in the subgroup of patients with severe obesities (BMI ≥40 kg/m²), as in those not losing significant body weight with diet and exercise alone during the initial one month run-in. However, in the limited number of Afro-American patients in the RIO studies (74 and 169 patients randomised to placebo and rimonabant 20 mg groups, respectively) weight loss was less pronounced (mean difference as compared to placebo was -2.9 kg).

Effect of rimonabant on dyslipidaemia

The patients included in the four studies could be considered to be representative for a broad population of obese patients with concurrent treated or untreated dyslipidaemia of the kind typically associated with overweight (low HDL-C and elevated triglycerides [TG]).

Mean HDL-C levels increased in all treatment groups, but in all studies the increase was greater in the rimonabant 20 mg group (mean differences 7.2 – 8.4% at one year, p<0.001) than in the placebo group. The differences between treatment groups were consistent in men and women. There was, however, a significantly less pronounced mean increase in Afro-Americans.

In the 4 RIO studies, the absolute TG levels decreased in the 20mg rimonabant group by -5.3 to -12.6%. In the placebo groups the mean triglyceride levels increased (by 7.3-8.3% in the RIO-Europe, Rio-NA and Rio-Diabetes studies) or remained stable (-0.2% in the RIO-lipids study). The decreases in the 20 mg group, when compared with placebo, were similar across the studies, with differences being 12.4 to 15.1% in non-diabetic patients in the ITT population (LOCF) (p<0.001). In diabetic patients the difference, compared with placebo, was 16.4%. The results were consistent in patients with elevated or normal TG at baseline. Generally the effects of rimonabant on HDL-C and triglycerides reached a plateau after approximately 36 week's of treatment.

The total-C and LDL-C remained unchanged in all groups in the RIO studies, taking into account the initial small drop in LDL-C observed during the run-in period. In RIO-Lipids LDL particle size was evaluated and a shift towards larger particles was noted.

The effects of rimonabant on glucose/insulin homeostasis

In the overall type 2 diabetes obese population (RIO-diabetes), with a mean HbA1c of 7.3% at baseline, the HbA1c decreased in the rimonabant 20 mg group by 0.6% compared with an increase of 0.1% in the placebo group, resulting in 0.7% improvement (p<0.01). The effects were similar in the metformin or sulfonylurea treated patients. A majority of patients were inadequately controlled at baseline. The 5 mg dose decreased HbA1c to a less pronounced extent. Fasting glucose was decreased by rimonabant 20 mg compared with placebo (mean difference -0.97 mmol/L; 95% CI; -1.30, -0.64). Insulin resistance as measured by HOMA (homeostasis model assessment, calculated from fasting glucose and insulin) decreased significantly in the rimonabant 20 mg group as compared to placebo.

In the 3 studies of non-diabetic patients there were 774 patients with impaired fasting glycaemia, i.e. fasting glucose (FG)≥5.55 mmol/L or diabetic FG (>6.99 mmol/L) at baseline. The mean difference in FG between the pooled 20 mg treatment groups and the placebo groups was -0.10 mmol/L (95% CI; -0.22, 0.03). Fasting insulin was higher than in the general population at baseline (around 16 µIU/mL). There was no change in the placebo group after one year, whereas insulin decreased by 3 µIU/mL in the pooled rimonabant 20 mg group (p = 0.002 in pooled studies).

In the subgroup of 258 prediabetic patients identified in the RIO-Europe and RIO-Lipids studies by the oral glucose tolerance test the glucose level at 30 minutes after the glucose load was lower in the pooled rimonabant 20 mg groups than in the placebo groups at one year (mean difference -0.89 mmol/L, 95% CI; -1.39, -0.39, p<0.001). No difference between groups was seen at 120 minutes. Mean insulin levels were

lower in the rimonabant 20 mg groups at 30 and 120 minutes after the glucose load compared with placebo.

In patients with normal FG at baseline no significant differences in FG between treatment groups were found at one year. However, in patients with normal FG both fasting insulin levels and HOMA levels were significantly reduced in the pooled 20 mg group as compared to placebo after one year.

Effect of rimonabant on blood pressure (BP)

In the subgroup of 555 patients who had elevated BP at baseline, defined as either SBP ≥140 mmHg or DBP ≥90 mmHg, decreases in SBP and DBP were observed at one year. Systolic blood pressure decreased by 8.5 mmHg in the rimonabant group and 6.9 mmHg in the placebo group. The decrease in DBP was 5.6 mmHg in the rimonabant 20 mg group versus -3.5 mmHg in the placebo group (p = 0.009). These changes were consistent with the observed body weight loss. In patients followed for two years no significant difference in blood pressure was seen between the rimonabant and placebo groups. In patients with normal BP at baseline, rimonabant 20 mg had no significant effects on BP.

Effects on the percentage of patients meeting the criteria for the metabolic syndrome

In the 20 mg groups, the percentages of patients having metabolic syndrome at endpoint were lower than in the placebo groups in the 4 RIO studies, see table 7 below.

Table 7: % of patients meeting the criteria for metabolic syndrome at baseline and at Year 1

		RIO-North America		RIO-Europe		RIO-Lipids		RIO-Diabetes	
		Placebo (N=607)	20 mg (N=1219)	Placebo (N=305)	20 mg (N=599)	Placebo (N=342)	20 mg (N=346)	Placebo (N=348)	20 mg (N=339)
Metabolic syndrome (ATPIII)									
Baseline	N	530	1081	271	540	310	314	316	318
	n (%)	168 (31.7)	376 (34.8)	108 (39.9)	228 (42.2)	161 (51.9)	166 (52.9)	251 (79.4)	252 (79.2)
Year 1	n (%)	155 (29.2)	229 (21.2)	85 (31.4)	106 (19.6)	127 (41.0)	81 (25.8)	232 (73.4)	204 (64.2)
	Odds ratio		0.541		0.440		0.429		0.597
	95% C.I.		(0.415,0.706)		(0.303,0.638)		(0.295,0.623)		(0.412,0.866)
	p vs placebo		<0.001		<0.001		<0.001		0.007

Quality of life measurements

In the IWQOL-Lite (Impact on Weight on Quality of Life-Lite) instrument significantly higher values were obtained in the physical functioning and self-esteem domains and in total scores in the 20 mg rimonabant groups as compared to placebo. There were also tendencies for improvements which became significant as compared to placebo in the pooled population for the other 3 domains (Sexual life, Public distress and Work). In the SF-36 instrument significant improvements in physical functioning and general health as compared to placebo were observed. On the other hand a trend for a less favourable emotional health and a significantly worse mental health situation in the rimonabant 20 mg group, as compared to placebo, was recorded.

Relationship between body weight loss and metabolic effects of rimonabant

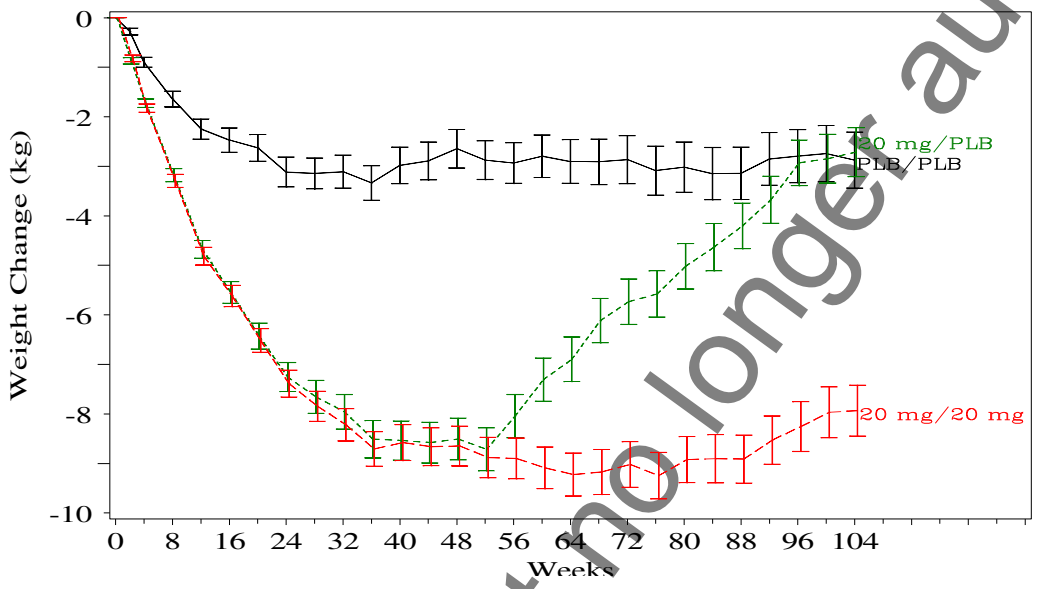
Four different methods were applied to investigate the relationship between metabolic changes and weight loss: comparison of changes in metabolic parameters over time versus changes in body weight, comparison of effects of rimonabant on metabolic parameters across weight change categories, assessment of metabolic changes in the population from the STRATUS development, and statistical (regression) analysis of the relationship between body weight loss and metabolic effects. It is estimated that approximately half of the mean improvements in HbA1c, HDL-C and triglycerides in patients receiving rimonabant 20 mg was beyond that expected from weight loss alone. In type 2 diabetes inadequately controlled at baseline approximately 50% of the total reduction in HbA1c levels (0.8%) was estimated to be independent of weight reduction. The magnitude of the estimated independent effects on lipids, was 3.6% change from baseline HDL-C (1.22) and 6.5% change from baseline triglycerides.

Efficacy results at 2 years

The body weight loss was essentially maintained in the 2 studies (RIO-Europe and RIO-North America) where patients received the treatment for up to 2 years.

In RIO-North America patients on rimonabant 20 mg were re-randomised to placebo or rimonabant 20 mg after one year and followed for an additional year. The body weight increased on average to levels similar to those treated with placebo/placebo for two years (see Figure 2 below). Available data do not indicate a rebound phenomenon.

Figure 2 RIO-North America: body weight change (kg) by visit at 2 years (mean ± SEM) - ITT population



SMOKING CESSATION

One phase II study (ACT4389), three short-term (10 weeks) phase III studies (STRATUS-US/ STRATUS-EU/ STRATUS-META), and one long-term (one year) phase III study (STRATUS-WW) were carried out to demonstrate efficacy and safety of rimonabant as an aid to smoking cessation. (See below Table 8.)

Table 8: Overview of submitted studies in smoking cessation

Main Studies	**Design**	**Treatment (QD)**	**Duration**	**Follow up off drug**	**Assessments**
STRATUS-US US, 11 centres	Rd, Db, Pl, Parallel group (3) design	Placebo Rimonabant 5 mg, Rimonabant 20 mg,	10 weeks	40 weeks	*Primary*: Abstinence during the last 4 weeks of treatment (self-report) *Secondary*: weight gain, craving
STRATUS-EU BE, DK, FR, ES, SE, SW, UK	Rd, Db, Pl, Parallel group (3) design	Placebo Rimonabant 5 mg, Rimonabant 20 mg,	10 weeks	40 weeks	*Primary*: Abstinence during the last 4 weeks of treatment (self-report) *Secondary*: weight gain, craving
STRATUS-META USA, 10 centres	Rd, Db, Pl, Parallel group (2) design	Placebo Rimonabant 20 mg,	10 weeks		*Primary:* Abstinence during the last 4 weeks of treatment (self-report) *Secondary*: weight gain, craving
Supportive Studies	**Design**	**Treatment arms**	**Duration**	**Follow up off drug**	**Assessments**
STRATUS-WW US, Canada, Australia	Rd, Db, Parallel group (2) design *Re-randomization of responders (abstinence) at week 10,* Db, Pl, Parallel group (5) design	Rimonabant 5 mg, Rimonabant 20 mg, Rimonabant (20)/20 mg, Rimonabant (20)/5 mg, Rimonabant (20 mg)/Pl Rimonabant (5)/5 mg Rimonabant (5 mg)/Pl	10 weeks 42 weeks	 52 weeks	*Primary:* Abstinence during the last 4 weeks of treatment (self-report) *Secondary*: weight gain, craving *Primary:* Relapse to smoking at week 32 (self report)
ACT4389 USA, 6 centres	Rd, Db, Pl, Parallel group (2) design, *phase II*	Pl Rimonabant 40 mg,	10 weeks	4 weeks	*Primary*: Abstinence during the last 4 weeks of treatment (self-report)

Db, double-blind; Pl, placebo-controlled; Rd, randomised

Dose-finding studies

The clinical efficacy of rimonabant in smoking cessation was first studied in a 10-week study (ACT 4389) comparing 40 mg to placebo in 370 subjects. 116/186 in the rimonabant group and 127/184 in the placebo group completed the 10-week treatment period. The number and percentage of patients who achieved the primary efficacy endpoint (prolonged abstinence during the last 4 weeks of treatment) in the rimonabant 40 mg group was significantly higher than in the placebo group (23.5% versus 13.1%, respectively; p = 0.0146; OR = 2.035, 95% CI: 1.176 – 3.522). The higher incidence of treatment discontinuations due to adverse events (AEs) observed with this dose compared with placebo [38 patients (20.8%) versus 10 (5.5%)], essentially due to gastrointestinal (nausea), central and peripheral nervous system (tremor, dizziness), and psychiatric disorder (anxiety, nervousness, depression) adverse events, led to consideration of lower doses in the following studies.

Main studies

A total of 7,164 patients were randomised in the three short term studies (main studies: STRATUS-US, -EU and -META studies) and one long-term study (supportive study: STRATUS-WW): the programme included 3,813 patients treated with rimonabant 20 mg, 2,534 patients treated with 5 mg and 789 patients in the placebo group. (See Table 8 above for more details.)

METHODS

Study participants, treatments

In the short-term studies the main inclusion criteria were: male and female, aged 18 years and older, who had smoked a mean of at least 10 cigarettes/day for a minimum of at least 2 months prior to treatment. They needed to be motivated to quit (score >6 on a 10-point visual analogue scale), and otherwise healthy as checked by physical examination, laboratory evaluation and ECG. Subjects were excluded if they were smoking other than regular nicotine containing cigarettes or marijuana at a regular base, if suffering from severe psychiatric illness (e.g. psychosis, depression, anxiety, alcohol or substance abuse/dependency, assessed by the MINI), or any clinically significant acute or chronic progressive somatic disease, or eating disorder. Subjects with a history of epilepsy, as well as subjects at high cardiovascular risk (uncontrolled hypertension, post-myocardial infarction) were also excluded. Female subjects were excluded when pregnant or lactating. Subjects were also excluded when they had used NRT, bupropion, counselling, or antidepressant therapy for more than 1 week, within 3 months prior to randomization, or systemic treatment on a chronic base (corticosteroids, antihistamines, or anti-obesity drugs).

In the STRATUS-WW the inclusion and exclusion criteria were similar to those in the main short-term studies.

In the short-term studies (STRATUS-US, -EU and –META studies) the patients were randomised while still smoking and were treated for two weeks prior to and eight weeks after the Target Quit Day (TQD); the patients were followed up for 40 weeks off drug. STRATUS-WW was a long term follow-up study: after ten weeks of double-blind treatment with rimonabant 5 mg/day (n=2016) or 20 mg/day (n=3023), patients who were abstinent were re-randomised to the active treatment or placebo for 42 weeks to evaluate maintenance of abstinence. Patients initially randomised to the 20 mg arm were re-randomised to 20 mg, 5 mg, or placebo. Patients initially randomised to 5 mg were re-randomised to 5 mg or placebo. The patients were followed up for 52 weeks off drug.

Outcomes/ endpoints

The primary efficacy endpoint in the three short-term studies was percentage of subjects with prolonged abstinence from smoking (not even a puff) at every visit during the last 4 weeks of treatment (week 7-10), as assessed by the subject's self-report and diary consultation, and confirmed by a CO content of the exhaled breath <10 ppm, and plasma cotinine <8 □g/l at 2 time points measured (week 8 and 10). Main secondary endpoints were: Change in body-weight [mean change from baseline in body-weight at the end of treatment in non-obese (BMI<30 kg/m2) subjects, categorized as decrease/no change/increase (decrease/increase defined as >5% difference from baseline)], and Decrease of craving [mean change from baseline at the end of treatment of the total score of the Questionnaire of Smoking Cessation Urges Brief form (QSU Brief)].

In the STRATUS-WW, the primary efficacy endpoint was time to smoking relapse from week 10 to week 32 [relapse was defined as: any 7 or more consecutive days of smoking (even a puff), or any 2 consecutive days of smoking 5 or more cigarettes per day (even a puff)]. Secondary endpoints included abstinence related endpoints (4-week prolonged abstinence, continuous abstinence, weekly point prevalence abstinence), body weight, craving, metabolic parameters. Time to relapse was also measured at week 52.

RESULTS

STRATUS-US, STRATUS-EU and STRATUS–META studies

The included subjects were middle-aged, with equivalent proportion of male and female patients. Most patients were Caucasian. Majority of the participants was enrolled in North America (84%).

Approximately 25% of the population across studies was obese (BMI ≥30 kg/m^2). Patients had been smoking regularly for about 24 to 27 years, and smoked an average of 23 cigarettes per day. The mean number of previous attempts to stop smoking ranged from approximately 3 in STRATUS-EU study to 6 in STRATUS-META study. The group of subjects above 64 years was small, only 55 subjects in the STRATUS-US, -EU and META together. The group of Afro-American subjects was also small (6%).
The efficacy of rimonabant as an aid to smoking cessation was observed in STRATUS-US, but the other two short-term studies failed to show significant differences between rimonabant and placebo (see table 9 below).

Table 9: Results from STRATUS-US, -EU and –META-studies

	STRATUS US			**STRATUS EU**			**STRATUS META**	
	Placebo (N=261)	**5 mg (N=262)**	***20 mg (N=261)***	**Placebo (N=260)**	**5 mg (N=256)**	**20 mg (N=267)**	**Placebo (N=268)**	**20 mg (N=262)**
Abstinent	42 (16.1%)	41 (15.6 %)	***72 (27.6%)***	51 (19.6%)	62 (24.2%)	66 (24.7%)	25 (9.3%)	36 (13.7%)
p vs placebo [a]		0.905	***0.002***		0.242	0.174		0.134
Odds ratios vs placebo		0.967	***1.986***		1.310	1.346		1.548
95% CI		(0.605, 1.546)	***(1.296, 3.046)***		(0.861, 1.991)	(0.890, 2.035)		(0.901, 2.661)

[a] p-values come from Fisher's exact test

The prespecified pooled analysis of prolonged abstinence data from these short-term studies suggested that rimonabant 20 mg was associated with greater efficacy compared with placebo (rimonabant 20 mg: 22.0%, placebo: 15.0%, p = 0.0003, OR = 1.610, 95% CI: 1.241, 2.088). A total of 47% more patients achieved abstinence with rimonabant 20 mg than with placebo.
The OR for smoking cessation with rimonabant was between 1.4 and 1.6, which places rimonabant at the lower end of the efficacy spectrum compared with conventional treatment modalities.

During the procedure the applicant submitted results of a follow-up of about one year of subjects from the short term studies. The STRATUS-US study patients treated with rimonabant 20 mg during the initial 10 weeks continued to show a statistically significant improvement in abstinence at 1 year (p=0.021); similarly, the STRATUS-EU results at 1-year remained consistent with those observed at 10 weeks, i.e. not significant. (See Tables 10 and 11 below.)

Table 10: Point prevalence abstinence at end-of-treatment visit (day 70) and end-of-study visit (day 350), in the STRATUS-US-study

Point Prevalence abstinence		**Placebo (N=261)**	**Rimonabant 5 mg (N=262)**	**Rimonabant 20 mg (N=261)**
Day70	n (%)	49 (18.8)	50 (19.1)	76 (29.1)
	p vs placebo		1.000	0.008
Day350	n (%)	30 (11.5)	34 (13.0)	50 (19.2)
	p vs placebo		0.689	0.021

Table 11: Point prevalence abstinence at end-of-treatment visit (day 70) and end-of-study visit (day 350), in the STRATUS-EU-study

Point Prevalence abstinence		Placebo (N=260)		Rimonabant 5 mg (N=256)		Rimonabant 20 mg (N=267)	
Day70	n (%)	59	(22.7%)	71	(27.7%)	78	(29.2%)
	p vs placebo			0.190		0.092	
Day350	n (%)	49	(18.8%)	49	(19.1%)	55	(20.6%)
	p vs placebo			1.000		0.662	

Thus, the short term effects seen in the –US study were relatively well maintained over one year, with a difference of 10.3% after 10 weeks compared to a difference of 7.7% after the additional 40 weeks of follow up.

STRATUS-WW study

The mean age of patients in STRATUS-WW-study was 44 (SD 11) years, the study included equivalent proportion of males and females, majority of the patients were Caucasian, the mean BMI was 28 kg/ m^2, the patients had been smoking for 26 (mean) years, and smoked an average of 23 cigarettes per day.

The results from STRATUS-WW-study are presented in Figure 3 and Table 12 below.

Figure 3: A summary of primary endpoint time to relapse for the 20 mg dose rimonabant.

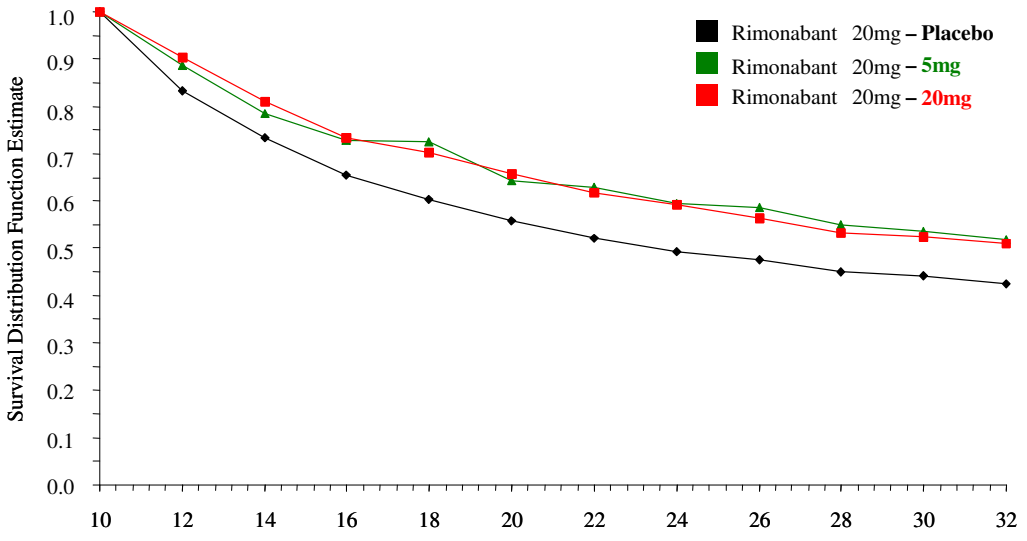


Table 12: Non-relapse rates at Week 32 (primary efficacy endpoint) and Week 52 (secondary efficacy endpoint) in the STRATUS-WW-study [N (%)], stratum 20 mg

Non-relapse rates	20 mg/PLB (N=342)	20 mg/5 mg (N=335)	20 mg/20 mg (N=340)
Week 32 (analyzed with the 1-year database)	145 (42.4%)	174 (51.9%)	174 (51.2%)
Odds ratio		1.468	1.424
95% confidence interval (CI)		(1.084, 1.988)	(1.053, 1.926)
p value versus placebo		0.009	0.009
Week 52	110 (32.2%)	140 (41.8%)	141 (41.5%)
Odds ratio		1.514	1.494
95% CI		(1.106, 2.073)	(1.093, 2.044)
p value versus placebo		0.005	0.005
Estimated Change from Week 32 to Week 52 with survival analysis approach	35/145 (24.1%)	34/174 (19.5%)	33/174 (19.0%)

[1] One additional patient was declared abstinent at Week 32 in the rimonabant 20 mg group at the time of analysis of the Week 52 data

A 10% difference in favour of rimonabant was observed for maintenance at Week 32 and Week 52, both for the 5 mg dose and the 20 mg dose versus placebo, in patients initially treated with rimonabant 20 mg. This corresponds for the 20 mg dose to a reduction in odds of relapse by approximately 30%. Both rimonabant 20 mg and 5 mg showed similar effects regarding maintenance of abstinence versus placebo in patients who initially stopped smoking with the 20 mg dose.
In addition, results after 102 weeks (off drug) are given in Table 13.

Table 13: Non-relapse rates at Week 102 in the STRATUS-WW-study [N (%)], stratum 20 mg

Non-relapse rates	20 mg/PLB (N=342)	20 mg/5 mg (N=335)	20 mg/20 mg (N=340)
Follow-up off-drug up to Week 102	81 (23.7%)	97 (29.0%)	106 (31.2%)
Odds ratio		1.313	1.460
95% CI		(0.932, 1.851)	(1.040, 2.048)
p value versus placebo		0.018	0.005

- Discussion on clinical efficacy

OBESITY

The demonstrated body weight reduction in overweight patients with additional cardiovascular risk factors and in obese patients and the effects on body weight related parameters obtained with rimonabant 20 mg were clinically relevant and maintained over time. Obese patients with type 2 diabetes and dyslipidaemia were specifically studied in separate studies and clinically relevant weight reductions were demonstrated also in these patient groups.

The CHMP does not currently accept metabolic syndrome as an instrument to identify a target population for pharmacological therapy. No generally accepted definition of the metabolic syndrome exists. No proper benefit/risk evaluation could be made for the long-term rimonabant treatment of patients with the proposed risk factor complex, as no outcome data with regard to clinically relevant events existed. Thus, the claim for pharmacological intervention based on a demonstrated reduction of the incidence of the metabolic syndrome (or of a general reduction of the incidence of the individual risk factor components) could not be accepted with current knowledge.

The effects of rimonabant on HDL-C, its subfractions and on triglycerides were interesting and they may indicate that rimonabant could reduce the risk for cardiovascular complications, which, however, remains

to be shown, as outcome data demonstrating a reduction of clinically relevant events were lacking. Furthermore, no comparative data with an active comparator product were available. Thus, a specific claim for treatment of dyslipidaemia could not be accepted; these effects were, however, considered of importance and are thus described in the SPC (5.1).

The indication as an adjunct treatment to diet and exercise to improve glycaemic control in treated type 2 diabetes patients suggested that in these patients with overweight there was more to gain than weight loss only, i.e. substantial glycaemic control. The total reduction of HbA1c in type 2 diabetes already treated with an oral anti-diabetic was 0.7% with rimonabant (as compared to placebo), which was judged to be a clinically relevant reduction. However, the significant interaction between weight loss and treatment with respect to HbA1c (%) allowed no straight forward interpretation of the main effect, i.e. reduction of HbA1c(%) corrected for weight loss; hence the independent effect of rimonabant on HbA1c was questioned by the CHMP. Therefore the applicant carried out extensive analyses, which demonstrated that there was, indeed, an effect on HbA1c that was independent of weight loss. It was difficult to exactly define the size of this effect (and will be the same also in larger studies), but it was agreed that the over-all HbA1c reducing effect was the most relevant effect from clinical perspective. Overall, the beneficial effects of combined weight reduction and improved glucose regulation (which is difficult to achieve in patients failing on metformin treatment with the treatment alternatives available today) could be expected to be greater in type 2 diabetes patients than in a general overweight population. However, no prospective confirmatory trial focusing on patients failing on OAD was performed. Also, no study on rimonabant monotherapy in type 2 diabetes patients was carried out. Thus, a separate indication for treatment of type 2 diabetes was not currently justified. Furthermore, treatment of overweight in patients with type 2 diabetes was already included in an indication for treatment of overweight patients with additional risk factors. It was agreed with the applicant that rimonabant could not be directly compared with classical OAD agents. A short description of the RIO-diabetes study results are described in the SPC (5.1).

Further, in the major dose-finding study the high withdrawal rate in combination with the rather small efficacy difference between the 10 and 20 mg groups, together with a tendency for a higher incidence of adverse reactions in the 20 mg group (nausea, diarrhoea, dizziness), resulted in remaining uncertainty whether 20 mg is the most optimal dose. The Applicant committed to further investigate (as a post-approval follow-up measure) the efficacy and safety of a 10 mg dose in patients not tolerating 20 mg due to side effects or as a long-term treatment to maintain the effects initially obtained with a 20 mg dose.

SMOKING CESSATION

The selection of doses (5, 20, and 40mg/day of rimonabant) for the different smoking studies was based on pharmacokinetic, safety and tolerability data of rimonabant in healthy volunteers. The maximal tolerated dose in those studies was 60 mg/day of rimonabant. Subsequently, the dose of 40 mg/day of rimonabant was chosen for the phase II smoking cessation study (ACT4389). No other doses were included in the phase II study, indicating that no formal phase II dose-finding studies were performed in the target population. Subsequently, based on efficacy and tolerability of rimonabant 40 mg/day in the ACT4389 study, and experience with the 20 mg/day dose in the obesity studies, the 5 and 20 mg doses were selected for the confirmatory phase III trials.

Only one of the three short-term phase III studies (STRATUS-US) was positive on all conditions, i.e. prolonged abstinence after 10 weeks treatment, and sustained abstinence at 1 year off drug. The other two studies were negative and thereby raised the question which study(ies) should be regarded as outlier(s). The pooled analysis of the short-term studies, as well as data from the study with 40 mg dose provided evidence that rimonabant had, indeed, positive effect in smoking cessation. The randomized withdrawal study was also positive with regard to maintenance treatment; however, the data could be regarded only as supportive. Overall, based on the totality of data it was concluded that an effect on smoking cessation had been demonstrated. The magnitude of the effect on smoking cessation was, however, difficult to

estimate. The variability in the results from the short-term studies indicated that the effect size may be marginal. Furthermore, there were remaining uncertainties regarding the optimal dose, duration of treatment and whether the dose could be decreased after an initial treatment period in cases where longer treatment is considered justified.

Clinical safety

- Patient exposure

The rimonabant clinical development program included 49 completed clinical studies, involving a total of 16,120 subjects or patients. There were 36 phase I studies and five phase II studies, in addition to a large phase III program, composed of two major sets of studies (four RIO studies and four STRATUS studies), which was carried out in the indications of body weight management and related metabolic disorders (6,625 patients), and aid to and maintenance of smoking cessation (7,136 patients), respectively (see Table 14 below). These studies were designed for assessing drug safety, i.e., randomised, double-blind, placebo-controlled and parallel group studies, and a substantial number of rimonabant-treated patients were exposed to either rimonabant 5 mg or 20 mg for one year or up to two years (in RIO studies) or for ten weeks or up to 32 weeks (in STRATUS studies; safety data between week 33 and week 52 were submitted during the procedure).

Table 14: Safety population exposed to rimonabant

	N studies	N exposed to rimonabant	Dose of rimonabant	Duration
Phase 1 studies				
Single dose studies	21	579	1 to 300 mg	-
Repeated dose studies	15	449	1 to 90 mg	Up to 4 weeks
Sub-total	36	1028		
Phase II studies				
Obesity/energy expenditure	2	227	5, 10, 20 or 40 mg	Up to 16 weeks
Aid to smoking cessation	1	183	40 mg	10 weeks
Relapse in alcoholism	1	131	20 mg	12 weeks
Schizophrenia	1	72	20 mg	6 weeks
Sub-total	5	613		
Phase III studies				
RIO studies	4	5023	5 mg or 20 mg	Up to 2 years
STRATUS studies (short-term)	3	1308	5 mg or 20 mg	Up to 10 weeks
STRATUS study (medium-term)	1	5039	5 mg or 20 mg	Up to 52 weeks
Sub-total	8	11370		
Total	49	13011		

- Adverse events

The overall safety review of the combined phase III RIO + STRATUS programs showed that treatment emergent adverse events (TEAEs) were comparably reported across the three treatment groups (rimonabant 5mg, rimonabant 20mg, placebo). TEAEs commonly reported (≥2% of patients) during rimonabant administration were mostly of gastrointestinal (nausea, diarrhoea, vomiting, loose stools), nervous system (dizziness, disturbance in attention, somnolence) or psychiatric origin (insomnia, anxiety, depressive disorders, mood alterations, irritability).

The following Table 15 shows all treatment-emergent adverse reactions from the four placebo-controlled studies in patients treated for weight loss and related metabolic disorders that occurred at a rate of ≥ 1%, when these incidences were statistically significantly greater than the corresponding placebo rate or

considered clinically relevant. They are listed by treatment group and by first- and second-year study periods.

Table 15: Adverse Reactions ≥ 1% from Four Studies that Examined ZIMULTI 20 mg in Overweight and Obese Patients.

	Year 1 (4 studies)		Year 2 (2 studies)	
SYSTEM ORGAN CLASS Adverse events	**ZIMULTI 20 mg % of patients (N = 2503)**	**Placebo % of patients (N = 1602)**	**ZIMULTI 20 mg % of patients (N = 688)**	**Placebo % of patients (N = 466)**
INFECTIONS AND INFESTATIONS				
Upper Respiratory tract Infection	12.4	11.4	-	-
Gastroenteritis viral	3.6	2.9	-	-
Nasopharyngitis	-	-	10.3	8.8
Urinary tract infection	-	-	2.8	2.1
Gastroenteritis	-	-	2.5	1.1
PSYCHIATRIC DISORDERS				
Anxiety	5.6	2.4	-	-
Insomnia	5.4	3.2	-	-
Mood alterations with depressive symptoms	4.8	3.1	-	-
Depressive disorders	3.2	1.6	1.6	0.4
Irritability	1.9	0.6		
Parasomnia	1.5	0.2	-	-
Nervousness	1.2	0.2	-	-
Sleep disorders	1.0	0.4		
NERVOUS SYSTEM DISORDERS				
Dizziness	7.5	4.9	-	-
Memory loss	1.6	0.9	-	-
Hypoesthesia	1.6	0.6	-	-
Sciatica	1.0	0.4	-	-
VASCULAR DISORDERS				
Hot flush	1.9	0.7	-	-
GASTROINTESTINAL DISORDERS				
Nausea	11.9	4.9	2.8	1.7
Diarrhoea	6.3	4.8	-	-
Vomiting	4.0	2.2	2.0	1.3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Pruritus	1.2	0.5	-	-
Hyperhydrosis	1.2	0.5	-	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Tendonitis	2.1	1.0	-	-
Muscle cramp	1.4	1.0	-	-
Muscle spasms	1.0	0.5	-	-
Back pain	-	-	7.3	5.2
GENERAL DISORDERS				
Influenza	8.9	8.6	9.2	7.5
Asthenia/Fatigue	6.0	5.0	-	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Joint sprain	3.0	2.1	-	-
Contusion	2.2	0.6	2.2	0.6
Fall	1.9	1.4		

Depressive disorders reported with rimonabant 20 mg were usually mild or moderate in severity. Most of the cases resolved with the corrective measures undertaken, either discontinuation or anti-depressant treatment. Overall, psychiatric adverse events or adverse symptoms from the CNS were more common among rimonabant treated patients than among placebo treated. These adverse events were dose dependent, where the 5 mg dose showed adverse event frequencies comparable to placebo, but the 20 mg and 40 mg dose showing a considerably higher frequency.

TEAEs related to cognitive impairment such as sedation, somnolence and disturbance in attention were reported and were comparable across the 3 treatment groups (rimonabant 5 mg, 20 mg and placebo) in the 1-year pooled RIO data and in the 2-year pooled RIO data. In the placebo-controlled period of the STRATUS program (10-week pooled data and STRATUS-WW week 11 to week 32) there were no signs of sedative effects.

In clinical studies on smoking cessation, also the following adverse reactions were commonly reported: sinusitis/upper respiratory tract infection, decreased appetite, anorexia, asthenia/fatigue, dizziness, disturbance in attention, anxiety, insomnia, nervousness, nausea/vomiting, diarrhoea, dry mouth, stomach discomfort.

- Serious adverse event/ deaths/ other significant events

Deaths
A total of 13 deaths were reported out of the 16 120 subjects or patients involved in the 49 completed studies: 11 in the RIO program, equally distributed across groups (four in the rimonabant 20 mg group, three in the rimonabant 5 mg group and four in the placebo group), and two in the STRATUS program (both in the rimonabant 20 mg group). Fatal events were mostly of an intercurrent origin (seven cases) or of a cardiac origin in patients with heavy cardiovascular risk factors (four cases). The origin of the two remaining cases remained doubtful: a completed suicide in unclear circumstances and a cardiac arrest, with no cardiac lesions on autopsy, possibly linked to a long QT syndrome, pre-existing prior to any study drug intake. In addition, there was a cardiac related death, occurring three weeks post-completion of study treatment (10 week of rimonabant 5 mg then 42 weeks of placebo) in the 1-year data of STRATUS-WW.

Obesity
In the RIO program, serious adverse events (SAEs) were reported with similar incidence in the placebo group and rimonabant groups: 5.9% in the rimonabant 20mg group, 5.4% in the rimonabant 5mg group and 4.2% in the placebo group. In each treatment group, similar SAEs in similar System Organ Classes (SOCs) were reported.

The following SAEs were more frequently reported in the rimonabant 20 mg group than in the placebo group:

- 12 cases of psychiatric disorders (6 serious depressive disorder) in the rimonabant 20 mg group (0.5%), versus 2 cases in the placebo group (0.1%);
- 12 cases of cardiac disorders in the rimonabant 20 mg group (0.5%) versus 4 cases in the placebo group (0.2%); 2 cases resulted in death;
- 9 cases of urinary disorders in the rimonabant 20 mg group (0.4%) versus 2 cases in the placebo group (0.1%)
- 6 cases of road traffic accident in the rimonabant 20 mg group versus zero in the placebo group; 2 cases occurred in the context of sleepiness.
- 4 cases of fall in the rimonabant 20 mg group.

In the 2-year pooled data, new SAEs during the second-year exposure were occasionally reported in the rimonabant 20 mg group (1 or 2 patients each) and were less or comparably reported than during Year 1; two cases had a fatal outcome.

Smoking cessation
Only few serious TEAEs were observed throughout the short-term STRATUS studies (pooled data), percentages being 2.2% for the placebo group, 1.2% for the rimonabant 5 mg group, and 2.0% for the rimonabant 20 mg group. No serious events were of cardiovascular origin in the rimonabant treatment arms (high risk subjects were excluded from participation). The cases that were considered of clinical relevance and related to the study-drug were severe fatigue, major depression and gastroenteritis.

- Laboratory findings

In the combined RIO + STRATUS data, no laboratory safety concerns were detected in the main biological functions (liver, renal, hematology, electrolytes, metabolism) over time during the whole rimonabant treatment period (up to two years), and were comparable with placebo.

Effects on ECG
PKD 5237 was a single-centre, randomised, double-dummy, placebo controlled, four parallel group study in 128 male or female subjects assessing the effect on ECG parameters of rimonabant 20 mg and 60 mg compared to placebo and with moxifloxacin 400 mg as a positive control. Moxifloxacin produced clear and consistent QT/QTc interval increases compared with placebo. There was no evidence for a potential of rimonabant to prolong ventricular repolarisation. There was no significant relationship between the QT changes from baseline as measured by the Holter method or from extracted ECGs (with Bazett, Fridericia, or population-specific correction) and rimonabant plasma concentrations. There was some suggestion that the 60 mg dose may be associated with a slight increase (+6 bpm) in heart rate (HR), in healthy subjects.

Vital signs
The review of vital signs, including supine blood pressure (BP) and HR from phase I and II studies did not reveal any safety issues. When combining all phase III studies, there was a trend towards a decrease in supine BP in the rimonabant 20 mg group compared with placebo.

- Safety in special populations

No marked differences in terms of clinical safety were observed for elderly compared to younger patients, but elderly obese patients appeared to be more prone to develop dizziness or diarrhoea compared with either young or middle-aged obese patients in the rimonabant 20 mg group.
There were no marked differences in terms of safety between the two prominent ethnic sub-groups (Caucasian and Afro-American patients), apart from a lower incidence of nausea or somnolence observed in Afro-American patients.

- Discontinuation due to adverse events

The overall safety review of the combined phase III RIO + STRATUS programs showed that there was a higher rate of treatment discontinuations due to AE in the rimonabant 20 mg group (15.7%) compared to placebo (7.8%) (also observed in the individual RIO and STRATUS programs). In the RIO 1-year pooled data, the main TEAEs leading to discontinuations in the rimonabant 20 mg treated patients, reported in at least 0.5%, were: nausea, mood alterations with depressive symptoms, irritability, anxiety, insomnia and dizziness (see Table 16 below).

Table 16: Percentage of patients with TEAE leading to permanent treatment discontinuation - randomised and exposed patients - 1-year pooled RIO data

	Placebo (N=1602)	Rimonabant 5 mg (N=2520)	Rimonabant 20 mg (N=2503)
Any event	7.2%	8.8%	13.8%
Depressive disorders	0.8%	1.0%	1.9%
Nausea	0.1%	0.2%	1.4%
Mood alterations with depressive symptoms	0.6%	0.9%	1.0%
Anxiety	0.3%	0.3%	1.0%
Dizziness	<0.1%	0.2%	0.7%

- Discussion on clinical safety

The main safety issue was the psychiatric AEs, which caused concerns, especially since patients with current depressions were excluded from the clinical studies. The safety data in Table 16 above shows that there was a dose-response relation between the frequency of certain psychiatric adverse events and the dose of rimonabant.

The findings from the RIO-programme showed that half of depressive disorders were reported during the first 3 months of the studies, when weight loss was maximum. The number of events was increased in the body weight responder patients compared to the non-responders. In the STRATUS program (10-week pooled data), the probability of occurrence of e.g. anxiety peaked after the target quit day; however, this could be expected in the context of the nicotine withdrawal. The SPC contains warnings (4.4) related to use in patients with uncontrolled serious psychiatric illness such as a major depression, and in patients with ongoing antidepressant treatment. The effects on the central nervous system, including psychiatric events, are also one of the main issues in the risk management plan.

5. 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 (see Table 17 below).

Table 17: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Missing or limited information		
Children under the age of 18	Monitoring of rimonabant prescriptions	SPC 4.2: Not recommended for those <18 years of age. Customer care program
Pregnancy		SPC 4.6: Use in pregnancy not recommended. Non-clinical findings described in 5.3. Customer care program
Lactation		SPC 4.3 and 4.6: Contraindication in lactation. Non-clinical findings described in 5.3. Customer care program
Elderly patients	THIN and ARIC databases, disease registry Further clinical trials, Monitoring of rimonabant prescriptions	SPC 4.2, 4.4: Use with caution in those >75 years of age. Mentioned also in 5.1-5.2. Customer care program
Black, Afro-Americans and Asiatic patients	ARIC databases, Further clinical trials	SPC 4.4: Warning of lower exposure in blacks. 5.1-5.2: Description of PK/PD-effects in blacks and Japanese. Customer care program
Patients with hepatic impairment		SPC 4.2, 4.4: Caution of use in patients with moderate hepatic impairment; use in severe hepatic impairment not recommended. PK-data described in 5.2. Customer care program
Patients with renal impairment	Further clinical trial	SPC 4.2, 4.4: Use in severe renal impairment not recommended. PK-data described in 5.2. Customer care program
Use of concomitant medications: antidepressants and potent CYP 3A4 inhibitors	Monitoring of rimonabant prescriptions	SPC 4.4, 4.5: Warning of use with CYP 3A4-inhibitors and with anti-depressants. Customer care program
Potential and identified risks		
Depressive disorders	Specific reporting forms THIN and ARIC databases, disease registry Further clinical trials Special reporting in PSURs	SPC: Described as an adverse effect in 4.8. Customer care program
Convulsions	Specific reporting forms, disease registry Further clinical trials	SPC 4.4: Warning of use in patients treated for epilepsy. Non-clinical findings described in 5.3. Customer care program
Anxiety	THIN and ARIC databases, disease registry Further clinical trials Special reporting in PSURs	SPC: Described as an adverse effect in 4.8. Customer care program

Insomnia	Further clinical trials	SPC: Described as an adverse effect in 4.8. Customer care program
Dizziness	Further clinical trials	SPC: Described as an adverse effect in 4.8. Customer care program
Neurological sensory disturbance of skin	Further clinical trials	SPC: Described as an adverse effect in 4.8. Customer care program
Withdrawal syndrome	Further clinical trials	
Off-label use	THIN and ARIC databases, disease registry Monitoring of rimonabant prescriptions	Customer care program

THIN and ARIC databases, disease registry: THIN (The Health Improvement Network Database) is a computerised database of medical records from general practices in the UK; it will be used to evaluate incidence rates of e.g. cardiovascular diseases and depression, and to address any new safety issues. The applicant also committed to perform a full periodic follow-up study of the outcomes of rimonabant exposed and non-exposed patients. ARIC (Atherosclerosis Risk in Communities database) is a prospective cohort study of atherosclerosis and cardiovascular disease conducted in 4 US communities; it will be used to evaluate e.g. cardiovascular diseases and depression. Disease registry: the applicant will establish a disease registry in the US population to assess e.g. background incidence rates of adverse events, to describe concomitant drug use/ co-morbidities, and to compare adverse events among rimonabant users and non-users.

Customer Care program: To encourage that rimonabant is used in patients at risk for *health* reason while avoiding use for *cosmetic* reasons: a specific training for company representatives will be implemented in order to provide healthcare professionals with the appropriate information (e.g. by offering physicians simple ways to educate patients on the clinical benefits of therapy while setting treatment expectations; providing physicians and other healthcare professionals with regular, ongoing educational support tools that can assist their patients in reaching the goals they have established for them; integrating practical diet and exercise information and programmes for healthcare professionals and their patients for when they prescribe rimonabant, that is consistent with local treatment guidelines). This customer care program will include education for example on the use of rimonabant in pregnancy, lactation, elderly, blacks, Afro-Americans, Asiatic, patients with hepatic or renal impairment, and with concomitant antidepressants or potent CYP3A4 inhibitors; education will be provided also on depressive disorders, convulsions, anxiety, insomnia, dizziness and neurological sensory disturbances of the skin.

Monitoring rimonabant prescriptions: Specific surveys will be put in place in order to monitor the prescriptions of rimonabant especially to detect any misuse / off-label use of the drug, by analyzing data such as drug prescriptions, diagnosis information, demographic parameters (weight, height, waist circumference, medical history).

Further clinical trials: These will be carried out as part of the large life-cycle management clinical trial programme of rimonabant. Special focus will be given on neurological and psychiatric adverse events through scripted neuropsychiatric questions obtained at every visit or intermediate phone calls. Separate studies will be carried out in patients with severe renal impairment and some other ethnic groups than blacks.

Special reporting in PSURs: Post-marketing cases of depression and anxiety in patients concomitantly using antidepressants will be presented separately in PSURs.

The CHMP, having considered the data submitted in the application is of the opinion that some additional pharmacovigilance activities are needed apart from routine pharmacovigilance activities (see table 17 above).

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Quality aspects are satisfactory. There are no unresolved quality issues which could have a negative impact on the benefit/risk balance of the product.

Non-clinical pharmacology and toxicology

Rimonabant is a selective CB1 antagonist. It showed activity in several animal models for obesity and nicotine addiction. The safety pharmacology studies identified CNS (sedation, decreased muscle tone, a proconvulsant potential when combined with physical or chemical seizure inducers, or with stressful conditions) as a possible target for rimonabant.

The results of the pharmacokinetic studies revealed a consistent picture across the species with rapid oral absorption, a low to moderate bioavailability, wide distribution, high protein binding, extensive metabolism, long terminal half-life with bile/ faeces as the major excretory pathway. One of the major metabolic pathways was hydrolysis of the amide bond that binds the piperidine ring to the rest of the rimonabant molecule, producing a metabolite SR141715, which could, theoretically, release the piperidyl radical as N-aminopiperidine (NAP); this compound is mutagenic in bacteria and may have other genotoxic properties. Precise estimate of the risk for humans could not be made but the risk was most likely very low; the applicant committed to provide additional data on the issue as a post-approval follow-up measure. No signs of genotoxicity were observed in a standard *in vitro* package or in a mouse micronucleus test.

The results of the toxicology studies were consistent across species, with reduced weight gain, weight loss, and/or decreased food consumption. CNS-effects including clonic convulsions were seen at higher doses; these symptoms prompted a reduction of the dose levels in the later studies. There were signs of involvement of the liver, kidneys and bone marrow, but none of these provided clear-cut evidence of a direct toxicity of rimonabant. The tumour findings in the liver and female genital tract found in the long-term rat study were considered to be species specific and due to enzyme induction and a chronic hormonal imbalance with oestrogen stimulation, respectively. The finding of neuropil vacuolation and increased GFAP staining in rimonabant treated mice, which could be a signal of underlying neuropathology, was diminished by the lack of other signs of neuropathology.

The toxic profile of rimonabant was not fully characterised as the highest exposures to rimonabant in the non-clinical safety studies were similar to the expected exposure in humans after the therapeutic dose. Thus, the non-clinical studies could provide no reassurance regarding margins to the clinical exposure at present. Consequently, the safe use of rimonabant has to rely more on the clinical safety data and on the post-approval pharmacovigilance programme.

The most remarkable effects in the reproductive toxicity package were decreased viability index and pup growth pre-weaning. There were malformations in the rabbit embryo-foetal development studies (omphalocele and various CNS-malformations) that could be due to rimonabant. These findings resulted in a warning against the use of rimonabant during pregnancy, and in a contraindication during lactation.

Finally, the environmental impact of rimonabant needed further evaluation and additional studies; the applicant committed to carry out such studies as a follow-up measure.

Efficacy

Obesity

More than 6800 patients were included in the Phase II and Phase III clinical studies. The patients included in the Phase III trials followed a mildly reduced diet during the trial prescribed by a dietician and they were advised to increase their physical activity. Significant mean weight reductions from baseline to one year for rimonabant 20 mg versus placebo were demonstrated in the three studies conducted in non-diabetic patients, and in one study with type 2 diabetics. Rimonabant was effective in maintaining weight loss for up to two years. Most of the observed weight reduction was obtained within the first nine months of treatment. Rimonabant reduced the risk of weight regain. Treatment with rimonabant was associated with reductions in waist circumference, and with an increase in HDL-C and decrease in triglycerides; generally no significant effect on Total-C or LDL-C levels were seen. In the trial in type 2 diabetic patients who were overweight or obese treated with metformin or sulfonylurea an improvement in HbA1c was observed.

Smoking cessation

One of the three short-term Phase III studies was positive on all conditions, i.e. prolonged abstinence after 10 weeks treatment, and sustained abstinence at 1 year off drug. The other two studies were negative. The pooled analysis of these short-term studies, as well as data from the Phase II study with 40 mg dose and the randomized withdrawal study on maintenance treatment provided evidence that rimonabant had positive effect in smoking cessation. Overall, based on the totality of data it was concluded that an effect on smoking cessation had been demonstrated; however, the magnitude of this effect was difficult to estimate, and possibly marginal.

Safety

The main safety issue was the psychiatric AEs, which were considered to have important implications for the use of rimonabant, especially since patients with current depressions were excluded from the clinical studies. There was a dose-response relation between different depressive AEs and rimonabant treatment. Most of the patients with various kinds of depressive symptoms did eventually recover with or without anti-depressants drugs. All this is addressed in the SPC and risk management plan.

The most common side effects were anxiety, insomnia, mood alterations with depressive symptoms, depressive disorders, dizziness nausea, diarrhea, vomiting, asthenia/ fatigue.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant provided results of assessments carried out in cooperation with target patient groups on the package leaflet ('user consultation'), and the package leaflet was modified accordingly.

Risk-benefit assessment

Management of multiple cardiovascular risk factors in patients with metabolic syndrome:

The CHMP does not currently accept the metabolic syndrome as an instrument to identify a target population for pharmacological therapy. Even if diabetes, hyperlipidaemia and hypertension are recognised as factors that, especially in patients with abdominal obesity, increase the risk for cardiovascular diseases, no generally accepted definition of the metabolic syndrome exists. A claim for pharmacological intervention based on a demonstrated reduction of the incidence of individual risk factor components commonly included in different definitions of the metabolic syndrome cannot be accepted with current knowledge. There are several effective options for the treatment of diabetes, hyperlipidaemia and hypertension available today; therefore the existence of an unmet medical need is questioned. On

these grounds the benefit-risk assessment regarding an indication of "Management of multiple cardiovascular risk factors in patients with metabolic syndrome" is negative.

Weight reduction in obesity/ overweight:
The demonstrated body weight reduction in overweight patients with additional risk factors and in obese patients has been sufficiently demonstrated and the magnitude of these effects is clinically relevant and appears to be maintained over time. The benefit-risk assessment for this indication in overweight/obese patients is positive, also in light of the psychiatric AEs that may develop over time and the pre-clinical uncertainties that still exist.

Type 2 diabetes:
Extensive analyses performed by the applicant demonstrated that rimonabant had an effect on HbA1c independent of weight loss. The size of this effect remained uncertain, although it was large enough to be clinically relevant. The beneficial effects of a combined weight reduction and improved glucose regulation could be expected to be greater in patients with type 2 diabetes than in a general overweight population. The treatment alternatives in overweight type 2 diabetes patients failing on oral anti-diabetics are limited and the weight gain that almost inevitably occurs when these patients are given insulin is a common and important clinical problem. However, it is recognised that a prospective confirmatory trial with rimonabant focusing on patients failing on oral anti-diabetics is lacking. Also, no study on rimonabant monotherapy in type 2 diabetes was performed. Therefore, the benefit-risk assessment was currently negative for diabetes type 2-indication. However, these effects are described in 5.1 of the SPC.

Dyslipidaemia:
The effects of rimonabant on HDL-C, its subfractions and on triglycerides are interesting and they may indicate that rimonabant could reduce the risk for cardiovascular complications, which, however, has not been shown (no outcome data available). Furthermore, no comparative data with an active product were available. Therefore, the benefit-risk assessment for the treatment of dyslipidaemia is negative. However, these effects are described in 5.1 of the SPC.

Smoking cessation:
An effect on smoking cessation of rimonabant has been demonstrated, but based on current data the magnitude of this effect is difficult to assess. In addition, uncertainties in relation to posology remained; in light of the psychiatric AEs that may develop with time and the pre-clinical uncertainties, it is important to establish the optimal duration of treatment and optimal dose. In conclusion, the uncertainties regarding the magnitude of the effect and posology result in a negative benefit/risk assessment for this indication. Additional efficacy data, in particular during short-term treatment, would be needed to establish a positive benefit-risk ratio. The Applicant withdrew the claim for a smoking cessation indication before the oral explanation.

Risk management plan:
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that some further pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns (see 3.5).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ZIMULTI "as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s), such

as type 2 diabetes or dyslipidaemia (see *SPC* section 5.1 *of the Summary of Product Characteristics*[5]).”
was favourable and therefore recommended the granting of the marketing authorisation.

[5] *Italic text added for clarity*