European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/348364/2008

CHMP ASSESSMENT REPORT
FOR
Tredaptive

International Nonproprietary Name:
nicotinic acid / laropiprant
Procedure No. EMEA/H/C/889

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 25 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Tredaptive, through the centralised procedure under Article 3(2)a of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 January 2007.

The legal basis for this application refers to:

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

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

The applicant applied for the following indication: Tredaptive is indicated as adjunctive therapy to diet for use in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia:

- who are treated with a statin and could benefit from having Tredaptive added to their regimen,
- in whom a statin is considered inappropriate or not tolerated.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 24 February 2006. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Harald Enzmann Co-Rapporteur: Pieter de Graeff

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 25 June 2007.
- The procedure started on 20 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 October 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2007.
- During the meeting on 12-15 November 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 November 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 December 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 February 2008.
- During the CHMP meeting on 18-21 February 2008, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues on 4 April 2008.
- During the meeting on 21-24 April 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a

Marketing Authorisation to Tredaptive on 24 April 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 April 2008.

- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 3 July 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hypercholesterolaemia or mixed dyslipidemia should be treated as other known factors to reduce the risk for cardiovascular disease. Treatment is based on diet and lifestyle adjustment to reduce low density lipoprotein cholesterol (LDL-C), raise high density lipoprotein cholesterol (HDL-C) and if needed, reduce triglycerides (TG) and other lipids. If adjunctive medication is needed, statins are the medications of the first choice. Reduction in cardiovascular morbidity and mortality has been demonstrated in the past with nicotinic acid (also known as niacin) at a time when statins were not available yet. Adverse events (AEs) are its main limitation, in particular flushing, gastrointestinal symptoms and elevation of liver enzymes. For these reasons, its use in patients with dyslipidemia is mainly second or third line therapy in those patients who do not respond to statins or fibrates.

The use of nicotinic acid however has been limited by its tolerability. The most common adverse effect occurring during the treatment with nicotinic acid is flushing. Although the mechanism by which nicotinic acid induces flushing is not completely understood, observations suggest that blockade of the prostaglandin D2 (PGD_2) receptor, specifically the subtype 1 (DP_1), may suppress the flushing symptoms associated with nicotinic acid in the human. Importantly, although these flushing effects are mediated by the nicotinic acid receptor, they appear to be independent of the beneficial lipid-altering effects of nicotinic acid.

Treatment with nicotinic acid has been shown to reduce the risk of overall and cardiovascular morbidity and mortality, as well as to slow progression or promote regression of atherosclerotic lesions. The Coronary Drug Project, completed in 1975, assessed the safety and efficacy of nicotinic acid and other lipid-altering drugs in men 30 to 64 years old with a history of MI (Coronary Drug Project Research Group, 1975). Nicotinic acid showed a statistically significant benefit in decreasing nonfatal, recurrent MIs. The incidence of definite, non fatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo ($p<0.004$). Though total mortality was similar in the two groups at five years (24.4% with nicotinic acid versus 25.4% with placebo; p=N.S.), in a fifteen-year cumulative follow-up there were 11% (69) fewer deaths in the nicotinic acid group compared to the placebo cohort (52.0% versus 58.2%; p=0.0004) (Canner et al., 1986).

Based on the established nicotinic acid efficacy and risk-benefit profile the key objective of the prolonged release nicotinic acid and laropiprant programme was to demonstrate improved tolerability of nicotinic acid when laropiprant is added. A fixed dose combination tablet of prolonged release nicotinic acid with laropiprant, a selective antagonist of the PGD_2 receptor subtype 1 (DP_1), is intended to reduce these PGD_2 mediated flushes and improve the tolerability profile, while the lipid lowering properties are maintained.

Tredaptive is indicated for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL-C and TGs and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

Tredaptive should be used in patients in combination with hydroxy-methyl-glutaryl-Co-enzyme-A (HMG-CoA) reductase inhibitors (statins), when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with Tredaptive.

2.2 Quality aspects

Introduction

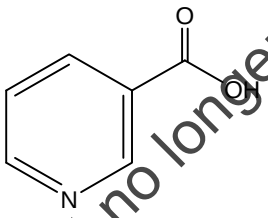
Tredaptive is presented as modified-release tablets containing two active substances. Each tablet contains 1000 mg of nicotinic acid and 20 mg of laropiprant. Tablets are bilayer and the lower layer is a prolonged release layer containing nicotinic acid, the upper layer is an immediate release layer containing laropiprant. The excipients used in the formulation of Tredaptive are well known excipients typically used in the tablet formulations such as hypromellose (E464), colloidal anhydrous silica (E551), sodium stearyl fumarate, hydroxypropylcellulose (E463), microcrystalline cellulose (E460), croscarmellose sodium, lactose monohydrate, magnesium stearate.

Tredaptive modified-release tablets are capsule-shaped, white to off-white with "552" debossed on one side. The tablets are supplied in Aclar/PVC or Alu/Alu blisters.

Active Substance

Nicotinic acid

Nicotinic acid, also known as niacin (USP name) or vitamin B_3 (synonym) is chemically designated as 3-pyridinecarboxylic acid (CAS), and has the following structure:



Nicotinic acid is white, not hygroscopic solid powder, sparingly soluble in water, soluble in boiling water and in boiling alcohol. Only crystalline form of nicotinic acid exists and no other polymorphic forms are known.

- Manufacture

The manufacturing process of nicotinic acid is a one step-step chemical synthesis process. A detailed description of the manufacturing process including process flow diagram and in process controls was provided in the restricted part of the Active Substance Master File (ASMF). The proposed manufacturing process has been adequately described, and critical steps with accompanying in-process controls have been identified. Appropriate specifications for the starting materials and reagents have been established.

In addition to the ASMF procedure a Certificate of Suitability with requirements of PhEur (CEP) for the active substance has also been provided.

The chemical structure of nicotinic acid has been confirmed by FT-IR, UV, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry (MS) and elemental analysis. The assessment of possible polymorphism has been performed using X-ray powder diffraction studies. It has been demonstrated that only crystalline form of nicotinic acid exists.

- Specification

The active substance specification is in line with PhEur monograph for nicotinic acid and with the USP monograph for nicotinic acid, and includes tests for identification (IR and UV), appearance, colour, transparency of the solution, melting point, heavy metals, chlorides, sulphated ash, residue on

ignition, water content, assay (titration), insoluble particles, magnetic particles, carbon content, impurities and related substances (HPLC and TLC), particle size distribution.

Analytical methods for control of the active substance are equivalent to the respective PhEur methods or are based on the PhEur methods with minor modifications. All analytical methods were described sufficiently. Validation data on HPLC method for impurity and the titration method for assay, as well as cross validation data of the titration method with the titration method described in the PhEur, and with the UV assay method described in the USP have been provided. It has been proven that the proposed analytical methods are suitable to control the quality of nicotinic acid.

Batch analysis data on three commercial scale batches have been provided. All batches complied with the requirements from the active substance specification.

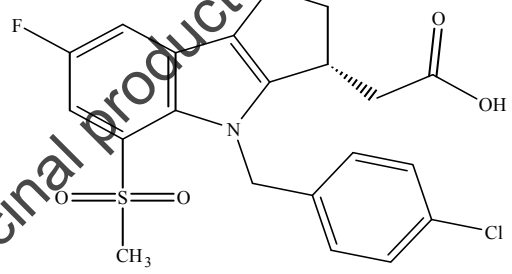
- Stability

Stability studies have been performed on 3 commercial scale batches of the active substance. Data was provided on batches stored up to 36 months at 25°C/60 % RH (long term stability studies) and 6 months at 40°C/75 % RH (accelerated conditions). Additionally the stability data on the active substance stored up to 36 months at -20°C was provided.

The stability data confirmed the re-test period proposed for nicotinic acid.

Laropiprant

Laropiprant is a selective PGD_2 receptor (DP_1) antagonist that reduces the incidence and severity of nicotinic acid-induced flushing. It is chemically designated as (3*R*)-4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*] indol-3-yl]acetic acid (CAS) and has the following structure:



Laropiprant is a white powder very soluble in acetone and acetonitrile, soluble in ethanol and methanol, and insoluble in water. The pH of saturated water solution is 6.1. Its pKa is 7.0 ± 0.2 (due to the carboxylic acid functional group). It has one chiral center, which has the R absolute configuration. Differential scanning calorimetry (DSC) showed a single melting endotherm with a peak temperature of 178.6°C. In temperatures close to 180°C decomposition (evaporation) was observed.
Extensive polymorph screening was performed and no other polymorphic forms were observed.

- Manufacture

Laropiprant is manufactured via a three-stage manufacturing process which comprises coupling of the starting materials followed by hydrogenation of the resulting intermediate to form the "crude salt of laropiprant". The final step involves the breaking of the salt and isolation (purification) of laropiprant drug substance.
The proposed manufacturing process has been adequately described, and critical steps with accompanying in-process controls have been identified. Appropriate specifications for the starting materials and reagents have been established.

In early development two types of manufacturing processes were used “first generation” enzymatic process, and “second generation” synthetic process. The second generation process is comparable with the current one which is an optimized “second generation” process with the same synthetic route.

Confirmation of the chemical structure of the active substance has been provided by ATR-FTIR, UV, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry (MS) and elemental analysis. The solid state structure of laropiprant was determined by single-crystal X-ray crystallography.

- Specification

The active substance specification includes tests for appearance, identity (IR), assay (HPLC), impurities (HPLC), chiral purity (HPLC), residual solvents (GC), water content, Ruthenium, heavy metals, sulphated ash and particle size.

Analytical methods have been sufficiently described and validated with regards to accuracy, intermediate precision and reproducibility, specificity, linearity, limit of detection (LOD) and limit of quantification (LOQ) where relevant. Particle size method has been validated regarding reproducibility and robustness. The HPLC methods for assay and impurities (including chiral purity) are sufficiently stability indicating.
The GC method for residual solvents was validated with regards to linearity, precision, specificity, accuracy, limits of quantification and detection, system suitability, and robustness.

Batch analysis data on batches of the active substance produced during the development of manufacturing process, clinical and safety trials and stability programs were presented.
The data includes results on five batches from the “first generation process” used for the early clinical and safety batches, eight batches from the “second generation process” used for other clinical trials and twelve batches from the “optimized process” for recent clinical and safety tests.
All batches complied with the requirements in the active substance specification.

- Stability

The stability studies have been performed on three batches of laropiprant after storage up to 24 months at 25°C/60 % RH (normal conditions) and at 40°C/75% RH (accelerated conditions). Additionally, data from forced degradation studies (exposure to elevated temperature, photolytic, acidic, basic, and oxidative conditions) has been provided to characterise potential degradation products and demonstrate the stability indicating nature of the HPLC analytical procedures.
As a supportive data results from stability studies on three pilot development batches manufactured according to “first generation“ process and stored up to 24 or 36 months have been provided.

The stability data confirmed the re-test period proposed for laropiprant.

Medicinal Product

- Pharmaceutical Development

The medicinal product has been developed as a bilayer tablets containing two separate layers (extended release with nicotinic acid and immediate release with laropiprant). Prolonged release layer with nicotinic acid is prepared by roller compaction and immediate release layer with laropiprant is prepared by high shear wet granulation.

During the development a Quality by Design approach was applied which allowed to
- o define the design space after identification of process parameter ranges that lead to a product of acceptable quality.
- o determine the initial control space, i.e. process parameter points or ranges to be used for routine manufacture
- o identify critical processing parameters, quality attributes and raw material property ranges required to ensure final tablet quality.

Layers with different content of laropiprant and excipients have been examined during the formulation development program. Optimisation studies of the lubrication system (magnesium stearate and sodium stearyl fumarate) resulted in optimal balance between bilayer adhesion and sticking propensity. Additional dissolution studies of single-layer tablets containing laropiprant granulation mixture showed the desired rapid release of laropiprant. After evaluation of different polymers, hypromellose was selected as the extended release polymer, which led to the target in-vitro dissolution rates of nicotinic acid. In addition to in-vitro dissolution, granule flow properties, particle size and hardness were examined in dependence to composition.

Formulation development was focused on optimization of extended release polymer levels to achieve consistent release of nicotinic acid at the target release rate, flow and compression properties of the granulations, and physical and chemical stability of the bilayer tablet. The key critical product attributes were derived from statistical analyses (Failure Modes Effects analysis). Design of experiments applied to the manufacturing process identified the critical process parameters and defined the limits necessary to avoid delamination of the bilayer tablets.

- Adventitious Agents

Among excipients used in the medicinal product only lactose monohydrate is of animal origin. Declarations from the lactose suppliers were provided, stating that the lactose was sourced from healthy animals under the same conditions as milk collected for human consumption.

Magnesium stearate and sodium stearyl fumarate used in the formulation are of vegetable origin.

- Manufacture of the Product

The medicinal product manufacturing process consists of five steps (1) laropiprant high shear granulation, (2) lubrication of laropiprant high shear granulation, (3) nicotinic acid roller compaction granulation, (4) lubrication of nicotinic acid granulation, (5) compression of bilayer tablets.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

In addition to the extensive studies of the manufacturing process and in-process controls during process development, the applicant has provided validation data on three commercial scale batches of the medicinal product.

- Product Specification

The product specification contains tests with suitable limits for appearance, identity of active substances (IR and HPLC), assay of laropiprant and nicotinic acid (HPLC), dissolution (HPLC), content uniformity (HPLC), degradation products (HPLC) and microbial bioburden.

The analytical methods have been sufficiently described and validated for the intended use. The discriminative power of the dissolution method was assessed for both laropiprant and nicotinic acid. The method has been adequately described and validated regarding specificity, working range, linearity, precision, accuracy, sample preparation and stability of solutions. The method is robust to changes of dissolution conditions as well as HPLC parameters. The analytical methods and acceptance criteria have been established to confirm the identity, purity and quality of the drug product and to ensure its suitability for their intended use.

Batch analyses results on pilot scale batches and production scale batches of the medicinal product indicate satisfactory uniformity and compliance with the agreed specification.

- Stability of the Product

The stability data was provided on three pilot scale batches, packed in the proposed packaging materials stored up to one year at long-term conditions (25°C/60 % RH) or at intermediate conditions (30°C/65 % RH) and up to six months at accelerated 40°C/75 % RH. No significant changes have been observed during the stability studies. In addition a supportive stability data on so-called "bridging batch" (production batch) stored up to thirteen weeks was provided. Results from a photo stability study performed according to ICH conditions have also been provided.

Based on the stability data the proposed shelf-life and storage conditions, as defined in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substances and medicinal product have been adequately described. Excipients used in the formulation of the medicinal product and the manufacturing process selected are typical for tablet formulations. The results of the tests indicate that the active substances and the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

2.3 Non-clinical aspects

Introduction

The main disadvantage of nicotinic acid as a lipid-modifying drug is the induction of cutaneous flushing. Evidence suggests that this side effect is mediated by the release of PGD_2 from cells in the skin, which binds to DP_1 receptors on vascular smooth muscles in the skin vasculature, resulting in vasodilatation. Provided non-clinical pharmacology documentation on nicotinic acid consists of literature publications only.

Laropiprant is a high affinity antagonist of DP_1 receptors and exerts antagonistic action with weaker affinity at the thromboxane A_2 (TXA_2) receptor (TP). Laropiprant antagonises the vasodilatory effect of nicotinic acid via inhibitory action on DP_1.

The non-clinical pharmacology documentation provided for laropripant consists of a standard set of original studies for new active compound in form of the *in vitro* receptor binding and inhibition studies.

All pivotal studies were performed in accordance with Good Laboratory Practise (GLP).
Non-pivotal, ancillary pharmacology/toxicology studies were stated as not fully GLP compliant and only summaries of the studies were provided, e.g. the individual datasets on the individual animals investigated were omitted. Nevertheless, a quality assurance statement is included confirming that a data audit in accordance with Merck-intern "Worldwide Non-clinical Quality Assurance Resources Standard Operating Procedures" was conducted.
Safety Studies were performed in accordance with current FDA GLP Regulations (21 CFR Part 58).

Pharmacology

Nicotinic acid has been used in the treatment of dyslipidaemia for over fifty years, during which the utility of several different animal models has attempted to explore the mechanism of action of this drug. As described in the literature, it is believed that the lipid lowering effect is achieved by multiple mechanisms, one of them being the ability of nicotinic acid to inhibit mobilisation of free fatty acids from adipose tissue and transiently reduce their serum concentration. Nicotinic acid lowers both serum TG and apolipoprotein B (Apo B), the major protein component of very low density lipoprotein (VLDL) and LDL. Given that LDL is formed as a result of VLDL catabolism, reduced hepatic VLDL output may contribute to the reduced serum total cholesterol (TC) and LDL-Cholesterol (LDL-C) observed with nicotinic acid therapy.

In the species where HDL metabolism has been examined, nicotinic acid generally lacks the effects seen in humans, with the possible exception of the mouse model, in which the human cholesterol ester transfer protein (CETP) transgene is expressed. Studies in both rabbits and mini-pigs indicate the possibility that nicotinic acid has benefits in atherosclerosis over and above the effects on serum lipids.

In vitro cell culture studies with various human and mouse monocytoid cell lines suggest that nicotinic acid induces production of PGD_2 and its metabolite, 15-$dPGJ_2$, in macrophages, the latter acting as an activator of PPARγ activity. This activation may potentially impact lipid metabolism and cholesterol efflux in these cells in a fashion that would be beneficial when treating atherosclerosis.

The mechanism by which nicotinic acid raises HDL-C is unclear, but is thought to be due to reduced HDL catabolism, since the kinetic turnover studies showed that nicotinic acid significantly reduces the fractional catabolic rate of both apoA-I and ^{125}I-labeled HDL.

A high affinity receptor for nicotinic acid has been described recently. The PR109a (also known as PUMA-G, HM74a or HM74b) is a $G_{\alpha i}$ -coupled, seven-transmembrane receptor expressed in adipose, spleen and lung tissues as well as in cultured macrophages stimulated with pro-inflammatory cytokines such as IFNγ. Studies in mice genetically engineered to lack GPR109a have shown that this receptor mediates both the serum FFA and TG-lowering effects of nicotinic acid in this species.

The presented non clinical studies show that laropiprant binds with high affinity to human DP_1 receptor (K_i of 0.57 ± 0.17 nM) and addition of 0.5% human serum albumin decreased the affinity at the human DP_1 about 2-fold (K_i of 1.07 ± 0.33 nM). The dissociation of laropiprant from the DP_1 receptor was confirmed to be much slower than its association. No agonistic activity on the DP_1 receptor was observed.

Examination of the DP-mediated effect of laropiprant *in vivo* was demonstrated using several animal models of asthma and seasonal allergic rhinitis, since studies in animals and humans established an association of PGD_2 and DP_1 in allergic airway diseases. Laropiprant was shown to be effective in animal models of allergic vasodilation in the upper airways: PGD_2 and *Ascaris*-antigen increased nasal airway resistance in cynomolgus monkeys and sheep. In three animal models of allergic bronchoconstriction laropiprant inhibited antigen-induced bronchoconstriction in guinea pigs and sheep incompletely, but did not show inhibition of antigen-bronchoconstriction in cynomolgus monkeys. Other possible effects of laropiprant on different DP_1 receptor mediated physiological responses have been investigated in additional studies with a more selective DP_1 antagonist related to laropiprant in a mouse model of atherosclerosis. The data did not reveal strong evidence for potential undesirable effects due to antagonistic effects on other DP_1 mediated physiological processes.

- Secondary pharmacodynamics

Although the key pharmacological effect of nicotinic acid is played by the released PGD_2 binding to the DP_1 receptors on the vascular smooth muscles in the skin vasculature, the literature data indicate that the formation of prostaglandin E_2 ($PGE_{2)}$) and its interaction with its EP_2 and EP_4 receptors may contribute as well.

The affinity of laropiprant to receptors other than DP_1 was examined in series of tests. Laropiprant binds to the human prostanoid G-protein coupled receptors in the following affinity order: DP_1 > TP > EP_2 > $CRTH_2$ >, $EP_{3\text{-III}}$, EP_1 > IP (prostanoid I receptor) > FP (prostanoid F receptor), EP_4. Based on the value of the dissociation constants, affinity of laropripant for the DP_1 receptor significantly exceeds that of the TP receptor: K_d = 0.03 nM and 10.9 nM for DP_1 for TP, respectively. The determined affinity to the EP_2 was markedly low, as well as the affinities to other prostanoid receptors. The selectivity of laropiprant for the DP_1-receptor is favourable with respect to its intended use.

The effects of laropiprant on platelet aggregation, examined as the ability of laropiprant to interact with the U46619 (a TXA_2 mimetic)-induced platelet aggregation in PRP from human and cynomolgus monkey, showed inhibition of U46619-induced platelet aggregation in a dose-dependent manner in human PRP with a mean inhibitory concentration 50% ($IC_{50)}$) of 0.77 ± 0.49 µM. In cynomolgus monkey PRP laropiprant inhibited U46619-induced platelet aggregation in a dose-dependent manner with a mean IC_{50} of 1.5 ± 2.1 µM. Association to and dissociation from TP receptor are fast ($T_{1/2[on]}$ and $T_{1/2[off]}$ of about 4 min).

Laropiprant has been investigated in a battery of 157 receptor binding and enzyme assays and affinities to all of these targets were markedly lower than those described above and did not raise safety concerns.

Three oxidative metabolites of laropiprant show affinities and potencies at human and dog DP_1 and TP, which are markedly lower than those for the parent compound, but these may contribute to the effects observed after laropiprant administration.

- Safety pharmacology programme

According to the limited literature data on the safety pharmacology of nicotinic acid, adverse side effects were observed in rats at doses of 0.5-2.0 mg/kg. There is an extensive experience with the use of nicotinic acid and thus, no further data are requested.

Safety studies with laropiprant investigating respiratory safety in rats, cardiovascular safety in conscious dogs and neurobehavioural safety in rats showed that maximum exposures of 71-90 times higher than the human exposure with the intended dose of 40 mg did not raise safety concerns.

In vitro measurements of recombinantly expressed hERG channels using standard whole-cell voltage-clamp techniques showed a reduction of 3-14% at 100 µM laropiprant concentration. Since the C_{max} in humans was determined as 3 µM and since laropiprant is bound to a very high degree (> 99 %) to the plasma proteins, the results do not raise significant safety concerns.

Additional studies investigating cardiovascular and autonomic effects of laropiprant in barbiturate-anesthetized dogs, renal function in conscious dogs, respiratory function, homeostasis, and platelet function in barbiturate-anesthetized dogs, gastrointestinal functions in dogs and mice, and neurobehavioural effects in mice do not indicate potential safety concerns.

- Pharmacodynamic drug interactions

No formal preclinical pharmacodynamic drug interaction studies were performed with nicotinic acid or laropiprant or with the combination of nicotinic acid and laropiprant. The rationale for this approach is acceptable, since the molecular targets of nicotinic acid are likely to be distinct from those of laropiprant. In addition, the animal models for nicotinic acid pharmacology, beyond its ability to

suppress plasma-free fatty acids and induce flushing, are not fully validated. Furthermore, clinical studies examining the key pharmacodynamic effects of nicotinic acid, its ability to reduce TG and LDL-C and to elevate HDL-C, demonstrate that co-administration of laropiprant has no effect on the lipid modifying properties.

Potential pharmacodynamic interactions with other medicines likely to be used concurrently with nicotinic acid/laropiprant, e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and HMG-CoA inhibitors, are considered unlikely.

Pharmacokinetics

Most pharmacokinetic studies were performed with laropiprant. The absence of the pharmacokinetic data for nicotinic acid alone and in combination with laropiprant was justified, since this has been evaluated extensively in humans, therefore no further non clinical studies were necessary.

Studies examining the absorption, distribution, metabolism, and excretion (ADME) of laropiprant were conducted in rat and dog, the two species selected also for the toxicological evaluation of the compound. For the purpose of interspecies comparisons between non-clinical animal models and humans, plasma protein binding, blood-to-plasma concentration ratio, metabolism, and excretion of laropiprant in humans were also discussed.

Based on *in vitro* studies on the metabolism of laropiprant and nicotinic acid, no interactions between the drugs are anticipated.

- Absorption

Following oral administration to male rats and dogs at 5, 25 and 100 mg/kg, absorption was rapid with peak plasma concentrations achieved between 0.8 to 2 hr. Plasma $AUC_{(0-\infty)}$ values increased in a dose proportional manner in rats, while in dogs, the plasma $AUC_{(0-\infty)}$ values were disproportionately high at the higher dose levels compared to the low dose. The oral bioavailability (F %) of laropiprant at 5 mg/kg was ~50 % in rats, ~70 % in dogs and ~8 % in monkeys. Following oral dosing to male cynomolgus monkeys at 2.9 mg/kg, the dose-normalized $AUC_{(0-\infty)}$ value was lower than that observed in rats and dogs, and the oral bioavailability was 8%.

- Distribution

Following intravenous (i.v.) administration at 1 and 5 mg/kg in male rats and dogs, and 2.9 mg/kg in male monkeys, laropiprant was cleared from the systemic circulation at a low to moderate rate (CL_p ~2, 5 and 8 mL/min/kg respectively). The volume of distribution at steady state (Vd_{ss}) ranged from 0.7 L/kg in rats to 3 L/kg in dogs, and the terminal half-life ($t_{1/2}$) was longer in rats and dogs (8 and 14 hr) than in monkeys (3 hr).

In a tissue distribution study conducted following the oral administration of a single dose of laropiprant (5 mg/kg) to rats, the drug was mainly distributed in the stomach, small and large intestine and the bile. The C_{max} was reached at approximately 2 hrs and declined steadily throughout 24 hrs post administration.
Laropiprant concentrations were not measurable in any central nervous system tissue, pineal gland, bone, or incisor pulp throughout the study period.

The *in vitro* reversible plasma protein binding in rats, dogs, mouse, rabbit, monkeys and humans was ~99%, and the *in vitro* blood-to-plasma concentration ratio was between 0.54 and 0.60 in the above named species.

The P-glycoprotein-mediated transport in vitro was evaluated in the LLC-PK1 cell line. The diffusion rate was relatively high for laropiprant (27 to 30 x 10^{-6} cm/sec). At substrate concentrations of 1, 5 and 10 μM, laropiprant was not a substrate of human MDR1, but was a substrate for mouse Mdr1a. In

addition, laropiprant was found to have no significant effect on the transport of digoxin, quinidine, verapamil, and vinblastine across LLCMDR1 cell monolayers.

- Metabolism

The metabolism of nicotinic acid has been described in humans, thus non clinical testing was not deemed necessary. However, two metabolism-interaction studies with nicotinic acid were conducted (see section Pharmacokinetic drug interactions).

The *in vitro* cytrochrome P 450 (CYP) and UDP-glucuronyl-transferase (UGT) metabolism of laropiprant was studied in mouse, rat, rabbit, dog, monkey and human liver microsomes, human intestinal microsomes and hepatocyte suspensions. The major metabolites identified in these media were hydroxy-, oxo-derivatives and the acyl glucuronide. Incubations of laropiprant with recombinant human CYPs suggested major involvement of CYP3A4, with a minor contribution from CYP2C9 isoforms. A comparison of K_m values obtained from recombinant human UGT isoforms indicated that UGT1A9 and UGT1A3 were the major isoforms responsible for the glucuronidation of laropiprant.

The *in vivo* studies were conducted in rats, dogs and humans. The major compound in the plasma of the animals was laropiprant, which was primarily eliminated by acyl glucuronidation.

In summary, laropiprant is metabolised primarily via acyl glucuronidation with a smaller component of oxidative metabolism.

- Excretion

Data on the excretion of laropiprant from one study in rats shows that the main excretion route is the faeces (97% of the dose) and studies in bile duct cannulated dogs and rats confirmed that laropiprant is excreted into faeces via bile. Approximately 2.3% of the dose is excreted in urine.

Clinical studies in humans indicate that the main route of excretion is via faeces (mean of 68% of total dose), with urinary excretion (mean of 22% of total dose) as a minor excretion route.

Placental transfer of orally administered laropiprant was investigated in pregnant rats at doses 100 or 400 mg/kg and rabbits at doses 25 or 125 mg/kg. The results demonstrated that laropiprant readily crosses placenta in both species. Nicotinic acid is actively transferred across the placenta.

The excretion of laropiprant into the milk of lactating rats was examined by measuring concentrations of parent drug in maternal plasma and milk on lactation day 14 following daily oral administration of laropiprant at 100 or 400 mg/kg from gestation day (GD) 6 to lactation day 14. Results of this investigation demonstrated excretion of circulating drug into the milk of lactating rats.

- Pharmacokinetic drug interactions

Nicotinic acid and its metabolites (nicotinuric acid, methyl nicotinamide and 1-methyl-2-pyridone-5-carboxamide) did not inhibit CYP1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4-mediated reactions in *in vitro* studies. The UGT1A1-mediated 3-glucuronidation of estradiol was not inhibited by nicotinic acid and its metabolites either. Based on these data, nicotinic acid would not be expected to cause drug interactions with drugs metabolised by these enzymes.

The *in vitro* assessment of laropiprant's ability to interact with CYP450 enzymes showed that the drug is a moderate CYP2C8 and a weak CYP2B6, CYP2C9 inhibitor. *In vitro* laropiprant did not demonstrate a time-dependent inhibition of CYP3A4 activity, but was shown to be its moderate inducer.

In a clinical drug-drug interaction study, laropiprant showed an interaction with midazolam. Plasma concentration of 1′-hydroxymidazolam was elevated in subjects receiving laropiprant, while midazolam plasma levels were not affected. Subsequently, laropiprant was evaluated *in vitro* as a

possible inhibitor of the glucuronidation of 1′-hydroxymidazolam by human liver microsomes and recombinant UDP-glucuronyltransferase (UGT) isoforms. Laropiprant was found to be a moderate inhibitor of UGT2B4 and 2B7, and a weak inhibitor of UGT1A4.

Furthermore, the inhibitory effects of clarithromycin, erythromycin, ketoconazole, and diltiazem (CYP3A4 inhibitors) on the formation of the acyl glucuronide of laropiprant were evaluated in human liver microsomes. The formation of the acyl glucuronide was inhibited in the presence of ketoconazole with an IC_{50} value of 44.5 μM. No inhibition of the formation of the acyl glucuronide was observed in the presence of clarithromycin, erythromycin or diltiazem at the evaluated concentrations. Based on these *in vitro* data, co-administration of clarithromycin, erythromycin or diltiazem would not be expected to have a clinically meaningful effect on laropiprant plasma exposures *in vivo*.

Toxicology

The toxicity profile of laropiprant was defined in oral single dose studies in mice and rats, and in oral and i.v. repeat dose studies of up to 53 weeks duration with laropiprant alone in mice, rats and dogs; laropiprant in combination with nicotinic acid in rats and dogs; and laropiprant in combination with nicotinic acid and simvastatin in rats and dogs.
The potential genotoxicity, carcinogenicity, reproductive toxicity, embryo- and developmental toxicity, local tolerance and other toxicity aspects were evaluated in the respective studies in several species.

- Single dose toxicity

The oral LD_{50} of nicotinic acid has been reported to be between 5000 to 7000 mg/kg in mice and rats. Animals died between 12 to 36 hours after dosing.

In single dose toxicity studies the approximate lethal dose of laropiprant was estimated as 1224 mg/kg/day in mice and 1591 mg/kg/day in rats. The exposure multiples for the lethal doses can be estimated as more than 400 for mice and 1000 for rats, when compared with the $AUC_{(0-\infty)}$ in humans after administration of the combination of 40 mg laropiprant and 2000 mg nicotinic acid.
In mice, after each dose increment the treatment-related effects were seen, including decreased activity, ptosis, bradypnea, lacrimation, sternal recumbancy and ataxia at 1 or 2 days after administration.
In rats, a 14-day observation period followed a single dose of laropiprant. The two rats that died showed signs of ptosis and salivation on day 1 before death at day 2. Surviving rats showed no treatment-related effects at day 14.

- Repeat dose toxicity (with toxicokinetics)

Oral repeat-dose toxicity studies of laropiprant alone, or in combination with nicotinic acid and/or simvastatin, was evaluated in mice, rats and dogs. For laropiprant alone, two studies of 5 and 14 weeks were conducted in mice, five studies of up to 27 weeks of duration were conducted in rats, and four studies of up to 53 weeks duration were conducted in dogs.

Laropiprant treatment caused death in mice at a dose of 750 mg/kg/day. Effects on the kidneys occurred in male mice from 250 mg/kg/day and in females from 500 mg/kg/day. Treatment-related effects on the liver were seen at all doses. A variety of treatment-related changes in haematological and serum biochemical parameters were also observed at all doses, including decrease in haemoglobin and haematocrit, and increase in total protein and cholesterol. In rats renal toxicity of laropiprant was apparent after 14 weeks at doses higher than 125 mg/kg/day in females and higher than 250 mg/kg/day in males. Increased liver weights and changes of urinalysis (e.g. staining, increased volume), serum biochemical parameters (e.g. increase of alkaline phosphatase, phosphorus, creatinine and decrease of glucose and chloride) and haematological parameters were apparent at doses higher than 250 mg/kg/day. In the 27 weeks study the no observed adverse effect level (NOAEL) was determined as 60 mg/kg/day. In dogs, orally administered doses above 5 mg/kg/day caused treatment related increase of ALT activity, whereas the i.v. administration of doses up to 6 mg/kg/day did not result in treatment

related findings. Transient post administration salivation was observed in rats and dogs, but was considered to be caused by the administration procedure and thus, without toxicological significance.

The AUC values obtained in the toxicity studies for laropiprant are sufficiently high when compared with the human exposure of 13 μM/l/hr during clinical use. The animal to human multiples at the NOAEL varied between 2 and 470 times which is considered sufficient.

The combination of laropiprant with nicotinic acid was investigated in rats and dogs in 26-27 weeks oral toxicity studies. In rats, post administration changes in serum levels of glucose, total protein and albumin and phosphorus, ketonuria and histomorphological changes in liver and kidney were observed. Although no NOAEL was determined, it was concluded that the no-effect level for laropiprant is 60 mg/kg/day in males and 180 mg/kg/day in females in this study, since findings typically associated with laropiprant could only be found above this level. In dogs, the bioavailability of laropiprant was much reduced and apart from vomiting starting at the lowest dose, only mild adverse effects were observed. No conclusions can be drawn about the possible toxicological effects of laropiprant in dogs, after combination therapy with nicotinic acid. The NOAEL for laropiprant was estimated to be 5 mg/kg/day in dogs.

The combination of laropiprant with nicotinic acid and simvastatin was investigated in rats and dogs. Rats showed salivation, decrease in body weight gain, cataract, increased neutrophils and monocytes, increased ALT, decreased triglycerides, and increased level of ketones in urine. No clear NOAEL was shown for the combination, although the NOAEL for laropiprant was estimated as 180 mg/kg/day, since no signs of toxicity typically associated with laropiprant were apparent. Dogs showed amongst other effects also redness of ears, abdomen, and genitalia, lacrimation, emesis and salivation, conjunctival vasodilation, miosis, chorioretinopathy, increase in ALT, decrease in cholesterol and triglycerides and retinopathy. The NOAEL for laropiprant was estimated as 5 mg/kg/day, although no clear NOAEL for the combination of laropiprant with simvastatin and nicotinic acid was shown.

In the toxicokinetic evaluation of the studies in rats, co-medication of laropiprant with nicotinic acid, or with nicotinic acid and simvastatin did not result in different $AUC_{(0-\infty)}$ levels of laropiprant. However, the AUC of nicotinic acid decreased by about 30% at higher dosing levels of laropiprant. In the additional presence of simvastatin the decrease in AUC levels of nicotinic acid was not observed. In dog, the $AUC_{(0-\infty)}$ of laropiprant was decreased by at least 50% in case of co-medication with nicotinic acid and simvastatin. Internal exposure of simvastatin was reduced in the presence of laropiprant. The interaction between laropiprant and nicotinic acid was not considered significant and relevant, since the observed toxicity related to nicotinic acid remained similar in both rat and dog despite differences in $AUC_{(0-\infty)}$. Furthermore, interactions between laropiprant and nicotinic acid and simvastatin have been evaluated in the clinical development program, and have no clinical relevance.

It is worth noting that effects on the liver were seen in all species tested. In mice these effects were evident from the lowest dose tested with an exposure multiple of 39. In rats, effects are seen from 180 mg/kg/day (exposure multiple 182), with or without nicotinic acid, but not in combination with simvastatin. In dogs, increased ALT was observed from 100 mg/kg/day with laropiprant alone or in combination with nicotinic acid, and from 25 mg/kg/day (exposure multiple 3) in combination with simvastatin. Considering these findings, monitoring of liver function tests is recommended in patients before initiation and periodically during the product administration, as stated in the Summary of product characteristics (SPC).

- Genotoxicity

Nicotinic acid is a well known and extensively tested substance and the amount of available data demonstrates the lack of clinically relevant genotoxicity.

A standard battery of genotoxicity studies were performed to assess the genotoxic potential of laropiprant, showing it to be devoid of any clinically relevant genotoxic potential.

Thus, both compounds were considered non-genotoxic.

- Carcinogenicity

The effect of the combination therapy was not studied, but the lack of carcinogenic potential in previous studies on nicotinic acid published in the literature justifies this omission.

Carcinogenic potential of laropiprant was investigated in two-year studies in rats and mice. No treatment related findings were reported in rats. In mice, however, statistically significant increase in tumours of testes was observed at the highest dose of 250 mg/kg/day compared to the control groups (tumour was detected in 5 mice compared to none in the two control groups). This increase is not considered to be related to the treatment, since the statistical significance was most probably caused by an atypical absence of spontaneous tumours of testes in the control groups in comparison with historical control data of the laboratory. The exposure multiple and safety margin at the NOAEL are considered sufficient to exclude a human safety concern at this dose.

- Reproduction Toxicity

No reproduction toxicity studies have been performed either with the combination of nicotinic acid and laropiprant or nicotinic acid alone. An overview of the literature data on the use of high dose nicotinic acid during pregnancy has been provided. Animal data on rats suggest no concern for teratogenic effects, but very limited data on human pregnancies indicate there might be a small increase in risk of congenital malformations. Thus, the use of high dose nicotinic acid should be avoided during pregnancy, as stated in the SPC.

In case of laropiprant, all main reproductive toxicity studies had been conducted in accordance with the Note for Guidance on Reproductive Toxicology: Detection of Toxicity to Reproduction for Medicinal Products (CHMP/ICH/386/95).

The laropiprant dosages used in the main reproductive toxicity studies in rats and rabbits were based on the results of dose-range-finding studies. Haematological and serum biochemical examinations revealed that laropiprant did not affect any haematological parameter in either species. Changes in biochemical parameters (dose-dependent aspartate aminotransferase (AST) and ALT increase) were seen in rabbits but not in rats.

Effects of laropiprant on *male and female fertility* were studied in rats. Treated males or females were mated with untreated females or males, respectively. Minimal toxicity (slight decrease in body weights and food consumption) was evident in treated females during the pre-mating period at 400 mg/kg/day dose. In treated males body weight gain was already reduced at 100 and 250 mg/kg/day dose groups. No effects were observed in the reproductive capacity of both genders. Litter parameters and sperm parameters were not affected by the treatment.

Embryo-foetal development studies with laropiprant were conducted on rats and rabbits. The combination therapy was not examined.
In rats, only the maternal body weight gain was decreased at high doses (400 mg/kg/day) with corresponding effects in the F1-generation (decreased body weight and incomplete ossification). No malformations were detected. In the rabbit study, clear toxic effects were seen at 125 mg/kg/day dose and post-implantation loss was also increased. Some malformations were detected in the F1-generation. In both species, laropiprant effects were associated with reduced maternal body weight gain (56%); nevertheless, the safety margins in both species are sufficiently high to consider a risk for human safety unlikely. The finding of "absent kidney" observed in rabbits was of some concern and it was questioned if it can be explained by the reduced number of litters and foetuses (3 abortions, 1 doe was found dead and another one was sacrificed) in the 5 mg/kg/day and 25mg/kg/day dosage groups. Historical control data on kidney malformations have been provided for the time period 2000-2007 and the submitted information justified the non-significance of the observed "absent kidney" effect.

Possible effects of laropiprant on the *prenatal and postnatal development* had been investigated in rats. In the F0-generation toxic effects were limited to doses of 400 mg/kg/day. Gestational body

weights were decreased, whereas lactation body weights were increased. Furthermore post-implantation loss was increased in this dosage group. In the F1-generation, pup mortality was increased during postnatal days 1 to 3. No major effects were seen in behavioural testing. The fertility index was decreased in the 400 mg/kg/day dose group (90% vs. 100% in the control group).
Overall, there were no effects on male or female fertility in rats from the use of laropiprant at doses up to 400 mg/kg/day. The safety margins for both species at the NOAEL are sufficiently high to consider a risk for human safety unlikely.

- Local tolerance

No new studies on local tolerance of nicotinic acid or the combination of nicotinic acid and laropiprant were submitted. This is accepted, as clinical experience with nicotinic acid over many years indicates a low risk for local irritation and toxicity studies with oral administration of the combination did not raise concerns in regard to local irritation.
Local tolerance of laropiprant was assessed in three test systems: *in vitro* bovine corneal opacity assay, EpiDerm human skin culture system and *in vivo* using rabbit skin. The results indicated no skin irritant potential, whereas a slight ocular irritation potential may be apparent, but this does not raise any concerns.

- Other toxicity studies

No other toxicity studies with nicotinic acid or with the combination of nicotinic acid and laropiprant were submitted. This is accepted, as there is an extensive clinical experience with nicotinic acid and there were no concerns identified suggesting that the combination would exhibit toxicological characteristics requiring further specific toxicity studies.

Antigenicity of laropiprant has been tested in two *in vivo* test systems. In both tests no sensitising potential was detected.

There was no indication of *immunotoxicity* observed for laropiprant in the routine repeat dose toxicity studies and there was no evidence of mechanism-based immunotoxicological risk. As such, in accord with ICH Guidance S8, no additional immunotoxicity studies were conducted

No additional *dependence* studies were conducted, since evidence of physical dependence or withdrawal was not observed in any of the repeat-dose toxicology studies or safety pharmacology studies evaluating neurobehavioral function. Additionally, laropiprant has undetectable levels of distribution in the brain.

Laropiprant was tested for *haemolytic* properties after intravenous application at clinically relevant concentration. No haemolytic activity was observed in washed human red blood cells (RBC).

No *phototoxicity* studies have been performed since the absorbance in the relevant parts of the spectrum is poor and no relevant distribution into the skin and eye have to be assumed.

The potential of laropiprant as *in inducer of microsomal enzyme activity* was investigated in liver homogenates of CD-1 mice and showed that the compound increases hepatic weights, induces fatty acyl-CoA oxidase activity, and increases CYP 3A and 4A activity.

Ecotoxicity/environmental risk assessment

As a vitamin, nicotinic acid is exempt from environmental testing.
The environmental risk of laropiprant was assessed according to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), June 2006. Laropiprant is not degradable, but it is not classified as persistent. There is no indication of a risk for bioaccumulation. The method used to determine log K_{OC} (adsorption coefficient) was considered insufficient and the commitment to conduct an OECD 106 study was recorded as a Follow Up

Measure. Laropiprant does not pose a risk to aquatic or sediment organisms, to micro-organisms in sewage sludge and to ground water.

2.4 Clinical aspects

Introduction

The clinical programme of Tredaptive included four phase II studies, four phase III studies and three phase II extension studies.

The Phase II programme consisted of 4 studies designed to address the following key objectives:
- Selection of the most appropriate flushing endpoints to assess nicotinic acid induced flushing
- Selection of the laropiprant dose
- Selection of the appropriate formulation of ER nicotinic acid for use in the combination tablet
- Demonstration of the lack of effect of laropiprant on lipids.

The four Phase III studies, which provide pivotal efficacy data for extended release nicotinic acid/laropiprant, set out the specific effects on lipids and flushing as their primary endpoints.

The claimed indication for Tredaptive is:
Adjunctive therapy to diet for use in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia:
- who are treated with a statin and could benefit from having Tredaptive added to their regimen;
- in whom a statin is considered inappropriate or not tolerated

The approved indication for Tredaptive is:
Tredaptive is indicated for the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

Tredaptive should be used in patients in combination with HMG-CoA reductase inhibitors (statins), when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with Tredaptive.

Formal Scientific Advice from CHMP was received in February 2006. The main issues discussed included: the design of the clinical development programme, in particular the pharmacokinetic, drug interaction studies and patient exposure, definition of indication, and the assessment and justification of the chronic use of the product. Overall, it is considered that the CHMP recommendations were adequately addressed and incorporated into the final clinical development programme.

GCP

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

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

Pharmacokinetics

The extended release formulation nicotinic acid (niacin)/laropiprant (also known as MK-0524A) is a fixed-dose combination of extended-release nicotinic acid with an immediate release layer of laropiprant (also known as MK-0524). The product has been formulated as a bilayer tablet consisting of 20 mg of laropiprant and 1g of ER nicotinic acid.

Because of the extensive and rapid metabolism of nicotinic acid in the liver (see section Metabolism and Elimination), its plasma levels are not a reliable measure of the rate or the extent of nicotinic acid absorption. Furthermore, liver is a potentially important site of action, and thus, it is crucial to measure endpoints that reflect the rate and extent of nicotinic acid delivered to the liver. Before reaching the systemic circulation, over 90% of orally absorbed nicotinic acid is metabolised to nicotinuric acid (NUA), N-methyl-nicotinamide (MNA), or N-methyl-2-pyridone-5-carboxamide (2PY). Therefore, the total amount of nicotinic acid and its metabolites excreted in urine and the total exposure to nicotinic acid and its metabolites in plasma provide a reliable measure of the extent of absorption of the oral dose. The NUA plasma levels are used for the estimation of nicotinic acid absorption rate due to the better correlation with the pharmacodynamic effects of the parent drug in comparison with nicotinic acid. The variability of NUA is substantially lower than that of nicotinic acid.

Thus, the early studies provide preliminary information primarily on plasma NUA as the primary endpoint, whereas the definitive phase III studies characterising the ER nicotinic acid in the ER nicotinic acid/laropiprant tablets use plasma NUA concentrations and the total urinary nicotinic acid and metabolites as the primary endpoints.

The pharmacokinetics of nicotinic acid is considered to be well known and the current evaluation is mainly dealing with the pharmacokinetics of laropiprant and its potential interactions with nicotinic acid.

Overall, 35 phase I studies were conducted to evaluate the biopharmaceutical and pharmacokinetic properties of ER nicotinic acid/laropiprant, including:

- biopharmaceutical studies with ER nicotinic acid/laropiprant
- laropiprant single dose studies in healthy subjects
- laropiprant multiple dose studies in healthy subjects
- laropiprant absorption, disposition, metabolism and excretion in humans
- laropiprant in special populations
- laropiprant drug interaction studies
- ER nicotinic acid/laropiprant drug interaction studies.

Commercially available NIACOR™ and NIASPAN™ nicotinic acid formulations were used in phase I studies. The phase II dose ranging studies were performed with NIASPAN™ and the evaluations were based on the suppression of NIASPAN™ induced flushing symptoms. In phase III studies, the comparability of the ER nicotinic acid formulation and NIASPAN™ in its activity to induce flushing symptoms was demonstrated in bridging studies, including investigations comparing the pharmacokinetic profiles of the two products.

One formulation of laropiprant has been used throughout the clinical development with minor alterations, either as separate tablets or as a part of a bilayer tablet. The laropiprant layer of the bilayer formulation used in phase III studies is identical with the proposed final market composition formulation, with the exception of minor alterations to excipients. These differences are not expected to affect the *in vivo* pharmacokinetics of laropiprant.

- Absorption

The absolute bioavailability of laropiprant in the ER nicotinic acid/laropiprant tablet was determined in a three period open-label clinical study in healthy adults as approximately 71%. The C_{max} was achieved in 1.9 hrs post oral administration. In addition, food does not appear to have a significant effect on laropiprant pharmacokinetics, the ratio of $AUC_{0-\infty}$ values in fed and fasted state is 0.94.

The oral bioavailability of nicotinic acid (based on the recovery of the dose in urine) as nicotinic acid and its major metabolites is estimated to be at least 69%. Administration in fed conditions has no major effect on the extent of absorption of nicotinic acid in ER nicotinic acid/laropiprant, but slows down the rate of nicotinic acid absorption.

As food does not have a clinically significant effect on the pharmacokinetics of laropiprant, nicotinic acid or the nicotinic acid metabolites, a specific dose recommendation with respect to food intake was deemed unnecessary. The SPC recommends taking the tablets with food. This, however, is for the reasons of tolerability and not bioavailability.

- Distribution

After i.v. administration of laropiprant concomitantly with nicotinic acid the volume of distribution and the elimination half life of laropiprant are approximately 70 L and 15 hrs, respectively. The determined volume of distribution is considered to be of moderate magnitude and exceeds the extra-cellular fluid space. This implies some uptake or binding to the cellular components of body tissue. Such assumption was confirmed by the *in vitro* studies in rats. The *in vitro* reversible plasma protein binding of laropiprant in humans was approximately 99% and its blood-to-plasma concentration ratio was estimated to be 0.55.

Based on data available in literature, nicotinic acid is less than 20% bound to serum proteins in humans. Nicotinic acid has been reported to be excreted in human breast milk. Plasma protein binding studies were not conducted with the combination of laropiprant and nicotinic acid since the affinity of nicotinic acid to plasma proteins was low and therefore, the likelihood of it displacing laropiprant and causing interactions is small.

- Metabolism and Elimination

Nicotinic acid undergoes extensive first-pass metabolism through two pathways that are dose and rate dependent:

1. Formation of nicotinamide adenine dinucleotide (NAD) and nicotinamide, which is further metabolised to MNA and to 2PY.
2. Conjugation with glycine forming NUA.

The first pathway predominates at low doses or at a low absorption rate. At higher doses or higher rates of absorption, the NAD pathway is saturable, and an increasing fraction of the oral dose reaches the bloodstream unchanged as nicotinic acid. The glycine conjugation pathway does not saturate across the clinically relevant dose range.

Nicotinic acid is excreted mainly in urine; approximately 69% of the total nicotinic acid dose can be recovered within 96 hrs post oral administration, accounting for 2% nicotinic acid, 7% NUA, 12% MNA and 46% 2PY.

Laropiprant is metabolised mainly *via* glucuronidation. The metabolic profile of laropiprant did not reveal the presence any significant levels of metabolites with strong DP activity (e.g. oxidative metabolites) in plasma. Only laropiprant and its glucuronide were detected as the main circulating forms, with the parent compound accounting for approximately 27% of the total exposure in plasma. Thus, any effect of laropiprant on the DP_1 receptors is mediated by laropiprant alone and not its metabolites.

The metabolism of laropiprant investigated *in vitro* using human liver microsomes and suspension of hepatocytes revealed formation of hydroxylated epimers and keto-derivative. Involvement of CYP 3A4 and CYP 2C9 in the oxidative metabolic pathway was confirmed, whereas several UGT isoforms were capable of generating the acyl glucuronide derivative.

Laropiprant is eliminated mainly in liver. Approximately 89.5% of administered dose could be recovered: 22% in urine and 68% in faeces. The acyl glucuronide was the primary compound detected in urine (64% of the total urinary material), with smaller contributions of two hydroxylated epimers and their glucuronic acid conjugates, the keto-derivative, and the parent compound. Unchanged laropiprant was the primary compound detected in faeces (73% of the total faecal material). The epimers of the hydroxylated metabolite and the keto-derivative were also detected in the faeces and accounted for 10% and 17% of the material, respectively.

Interconversion:
Laropiprant is a chiral molecule with one chiral centre. The active substance used in the fixed combination product is the *R*-enantiomer. Therefore, a concern related to a potential interconversion of the *R*- to the *S*-enantiomer has been raised. The supplied information on the results of the *in vitro* and *in vivo* stability testing indicated no interconversion of the examined *R*-enantiomer.

- Dose proportionality and time dependencies

The dose dependency was investigated over a wide range of single and multiple doses. No clinically significant deviation from linearity was detected between 3 mg to 400 mg doses after single or multiple dosing. No unexpected increase in the exposure was found after once daily dosing for 10 consecutive days; the minimal accumulation of approximately 30% for AUC and 10% for C_{max} averaged across all examined doses did not raise concern. In addition, only one strength of laropiprant is proposed to be marketed and thus, the linearity of the dose-dependency profile is not considered relevant.

- Special populations

Effects of intrinsic and extrinsic demographic factors on the pharmacokinetics of laropiprant were evaluated through 2 different types of analyses. Phase I studies were conducted to directly evaluate the effect of demographic and some other factors on laropiprant pharmacokinetics (gender, age, hepatic function, renal function, and food effect). Subsequently, a composite pharmacokinetic analysis was performed to evaluate the effect of gender, age, race, and body mass index on laropiprant pharmacokinetics in the phase I population. An evaluation of possible differences in the pharmacokinetics of laropiprant in the presence *versus* absence of ER nicotinic acid was also performed.

Results from both, the individual studies and the composite analysis, indicate that the demographic factors (age, gender, race and body mass index) do not clinically impact pharmacokinetics of laropiprant when administered as laropiprant alone or in combination with ER nicotinic acid. Thus no dose adjustment for laropiprant is warranted on this basis.

The data currently presented on pharmacokinetic of laropiprant do not include the information on pharmacokinetics in target population. Pharmacokinetic population analysis in such population is required and the submission of a plan to evaluate the pharmacokinetic of laropiprant in the target patients was taken up as a follow up measure.

While no clinically relevant effect of age on the pharmacokinetic of laropiprant or nicotinic acid was observed in the studies in the elderly, no specific evaluation has been conducted in children and adolescents.

In the population with severe renal insufficiency, a modest, but clinically insignificant increase in the AUC of laropiprant was observed. Severe renal insufficiency did not alter the C_{max} of laropiprant, but the apparent terminal half-life was prolonged. The effect of mild or moderate renal insufficiency on laropiprant pharmacokinetics was not evaluated in phase I studies, but given that no clinically meaningful impact was observed in severe renal insufficiency patients, a lack of significant effects in mild and moderate renal insufficiency can be expected. Based on the high degree of plasma protein binding, it is unlikely that laropiprant is dialyzable. As only 22% of the laropiprant dose is excreted *via* the kidney, renal insufficiency will most probably have only a minor effect on the pharmacokinetics.

Even though the pharmacokinetics of laropiprant was not markedly altered by severe renal insufficiency, nicotinic acid and its metabolites are primarily excreted by the kidney; thus, caution should be applied when ER nicotinic acid/laropiprant is administered to patients with renal insufficiency. The warning taken up in the SPC stating that Tredaptive should be used with caution in patients with renal dysfunction is based on the pharmacokinetics of nicotinic acid.

In studies with patients suffering from moderate hepatic insufficiency, a 3-fold increase in exposure of 40 mg single dose laropiprant was observed compared to healthy subjects. Furthermore, the exposure to the main metabolite (glucuronide) is increased. In addition, nicotinic acid is contraindicated in patients with significant liver dysfunction. Thus, the ER nicotinic acid/laropiprant combination product should not be administered to these patients. These findings are in line with the results of the study with mild liver insufficient patients and the contraindication warning has been incorporated into the SPC.

- Pharmacokinetic interaction studies

Studies of the hepatic metabolism of nicotinic acid were not performed, because these have been studied and reported in animals and humans in the past. *In vitro* drug interaction studies with the combination of laropiprant and nicotinic acid were not conducted, since each of the compounds was extensively studied to evaluate their maximum potential for drug interactions. These tests showed that laropiprant and nicotinic acid did not affect the common metabolic pathways, and thus, further combination studies would be unlikely to provide substantial information.

The *in vitro* metabolism laropiprant was studied in animal, human liver and human intestinal microsomes, and suspensions of freshly prepared or cryopreserved hepatocytes. Results indicate that laropiprant is not expected to alter the pharmacokinetics of co-administered drugs. In experiments with human liver microsomes laropiprant did not inhibit CYP1A2-, CYP2B6-, CYP2C9-, CYP2C19-, CYP2D6-, CYP2E1- and CYP3A4-mediated reactions and is not a substrate for, or an inhibitor of the human p-glycoprotein (p-gp). Laropiprant was a moderate inducer of CYP3A4 and has the potential to cause drug interactions *via* UGT1A1, 2B4, and 2B7 effects.

Interactions of laropiprant with other drugs were examined in a series of *in vivo* studies. Nicotinic acid did not influence the pharmacokinetics of laropiprant in a clinically significant way and vice versa. The interaction studies with midazolam, which is predominately metabolised by CYP3A4, demonstrate that laropiprant does not influence its metabolism, but inhibits the metabolism of the oxidative metabolite, 1-hydroxy-midazolam. This indicates that laropiprant significantly inhibits UGT2B4 and UGT2B7, since these enzymes appear to be further involved in the metabolism of 1-hydroxy-midazolam. However, additional data in support of the hypothesis that laropiprant is an inhibitor of UGT2B7 and of the consequent SPC statement are necessary. The commitment to conduct *in vitro* studies with UGT2B7 substrates has been included as a follow up measure. Depending on the results of the *in vitro* studies, further *in vivo* evaluations might be needed.

The lack of laropirant's effect on the CYP3A4 isoform was also confirmed in an interaction study with simvastatin. However, a different study examining the effect of simvastatin on ER nicotinic acid/laropiprant indicated a non negligible increase in relevant parameters of simvastatin; the mean AUC and C_{max} are increased by approximately 60% and 40%, respectively. It is implied that these parameters can rise in a similar magnitude in the elderly and thus, the increase may be additive. Since the currently provided data are not sufficient to exclude adverse effects on liver and/or muscle in the subgroup of patients >65 years, the incidence of such events (hepatic symptoms, abnormal liver function tests, myopathy/rhabdomyolysis tests) is to be monitored as stated in the Risk management plan (RMP). Data from elderly patients in the ongoing trial will be analysed and the commitment to provide CHMP with the DSMB recommendations of this study has been requested as a follow up measure.

The pharmacokinetics and pharmacodynamics of warfarin are not influenced by the co-administration of laropiprant. (*R*)-warfarin is metabolised by CYP3A4, 1A2 and 2C19 and (*S*)-warfarin preferably by CYP2C9, the results of this study confirm the observed *in vitro* data. Laropiprant does not appear to have an effect on the pharmacovigilance of digoxin. Administration of laropiprant with clarithromycin, a potent inhibitor of CYP3A4, is associated with a modest increase of laropiprant $AUC_{0-\infty}$ and C_{max} values, but this was not considered clinically important. Furthermore, laropiprant does not significantly influence the pharmacokinetics of rosiglitazone, which is primarily metabolised by CYP2C8. Administration of laropiprant 40 mg single daily dose combined with the oral

contraceptive containing ethinylestradiol and norelgestromin does not result in significant alterations of plasma levels of the contraceptive components.

Overall, the potentials for drug-drug interactions of both components of the proposed fixed combination have sufficiently been addressed in the provided programme or in the follow up measures, and are appropriately labelled.

Pharmacodynamics

The development programme was focused on establishing the pharmacodynamic properties of the new active substance laropiprant. The mode of action of laropiprant, including primary and secondary pharmacology has been investigated sufficiently. Since clinical efficacy regarding nicotinic acid is based on pharmacodynamic surrogate endpoints, the phase III programme provides further assessment of the pharmacodynamics (lipid efficacy and flushing) of the ER nicotinic acid component of the ER nicotinic acid/laropiprant tablet either when given alone or as a part of the combination product.

- Mechanism of action

Flushing symptoms include redness of the skin, sensation of warmth, itching and tingling. Nicotinic acid-induced flushing (NIF) is mediated primarily by PGD_2 released by skin cells. Animal studies showed that the PGD_2 receptor subtype 1 (DP_1) is an important mediator of the flushing induced by nicotinic acid.

Laropiprant is a potent and selective antagonist of DP_1 receptor. It also has the affinity to interact with thromboxane A_2 receptor (TP), although it is approximately 190-fold less potent when compared to DP_1. Activation of TP has been shown to induce platelet aggregation *in vitro*, whereas activation of human platelet DP_1 inhibits platelet aggregation. These *in vitro* data indicate that laropiprant may alter platelet function either by enhancement of platelet reactivity through DP_1 antagonism or by inhibition of platelet aggregation through TP antagonism.

- Primary and Secondary pharmacology

The primary pharmacology programme involved the examination of the effect of laropiprant on NIF symptoms (measured by Visual Analog Score (VAS) and intensity scores) and on nicotinic acid induced increases in skin blood flow, as measured by Laser Doppler Perfusion Imaging (LDPI). It was demonstrated that both, the symptom scores and skin blood flow measurements, show a dose dependent decrease in NIF with multiple dosing of laropiprant in the dose range of 5-300 mg. Administration of single and multiple doses of laropiprant can reduce flushing, especially when higher doses (100-300 mg) are used. The proposed dose of laropiprant in the final combination product appears to reduce flushing, but a real cut-off dose for maximum reduction of flushing is not apparent from the conducted studies. Differences between 30 mg laropiprant, 100 mg laropiprant and aspirin treatment were small and not significant, thus, questioning the claim that these dosages are significantly better in reducing flushing than aspirin. The results of the Maximum Overall Severity Symptoms Score (OSSS) test indicate that co-administration of aspirin and laropiprant does not seem to produce a major effect on flushing. Aspirin is currently used in the treatment of NIF.

Effect on platelet function is the key issue with respect to the secondary pharmacology of laropiprant. Since laropiprant has affinity to both, the DP_1 receptor and the thromboxane A_2 receptor, there is a possibility that laropiprant may alter platelet function. This can be demonstrated either as an enhancement of platelet reactivity through DP_1 antagonism, or as an inhibition of platelet aggregation through TP antagonism. No dose-dependent effect on PGD_2 stimulated cAMP in platelets aggregation was observed *ex vivo.* The collagen agonist-induced platelet aggregation showed a small increase in inhibition with a lower dose of laropiprant (60 mg), but the clinical meaning of these results is unclear. Results from studies examining the changes in the *in vivo* bleeding time are conflicting between the different studies. Clinically meaningful prolongation of bleeding time can only be expected with higher doses leading to C_{max} levels 3 times higher than the therapeutic doses. In summary, no clinically relevant effects on platelet mediated bleeding effects were noted at therapeutic concentrations of

laropiprant, but the lack of clear pharmacological results indicated the need for further research and clinical testing. New studies evaluating the effects of multiple doses of laropiprant on the antiplatelet effects of clopidogrel alone and clopidogrel and aspirin in combination and the effect of nicotinic acid and/or laropiprant on platelet aggregation and bleeding are in progress, and the results will be provided to the CHMP as a follow up measure.

Concomitant use with aspirin does not show additive effects on bleeding time when lower doses of laropiprant are used which is in line with the previous results. Furthermore, other possible effects of laropiprant due to the inhibition of different DP_1 receptor mediated physiological responses may play a role in the pathophysiological process of endothelial dysfunction potentially leading to atherosclerosis and subsequent cardiovascular events. Thus, a commitment to conduct regular review and evaluation of post-marketing reports within the PSURs and monitoring of clinical trial reports of adverse events related to inhibition of platelet function was included in the RMP.

Laropiprant was found to have no clinically relevant effect on QTc and no further investigations on this aspect were needed.

Phase II studies established that laropiprant doses of 18.75 mg - 150 mg were similarly effective in reducing flushing symptoms induced by 1 g nicotinic acid, and laropiprant doses of 37.5 mg - 300 mg were effective for NIF reduction after administration of 2 g of nicotinic acid.

Clinical efficacy

- Dose response studies

The efficacy of ER nicotinic acid/laropiprant was demonstrated in four phase II and phase III studies. The phase II programme aimed to select the most appropriate flushing endpoints, to assess nicotinic acid induced flushing, to select the dose of laropiprant, to select a formulation of ER nicotinic acid for use in the combination tablet, and to demonstrate that laropiprant has no effect on lipids.

Studies contributing to the clinical efficacy and safety of ER niacin/laropiprant

Study Nr.	Type of study	Treatment arms	Randomised	Endpoint	Duration
Dose finding					
P011	Randomised, db, pc	Niaspan 1g-2g with MK-0524 18.75-37.5mg to 150-300mg (6 groups)	412	Max GFSS during week 1	8 weeks
P032	Randomised, db, pc	Niaspan 2g with MK-0524 5 to 300mg	575	Max GFSS during week 1	1 week
FSQ validation					
P015	Randomised, db, pc, parallel	Week 1: N1 (Niacin 1g) vs P(lacebo) 1:1 ratio Week 1; 2-4; 5-8 N1/N1/N2 N1/N1/N1 N1/P/P P/P/P 1:1:1:1 ratio	180	Max GFSS during week 1 # days/week with moderate or greater GFSS (≥ 4) across treatment period	8 weeks
Lipid efficacy studies					
P020	Randomised, db, pc	Mk-0524A 1g/2g Niacin 1g/2g Placebo 3:2:1 ratio	1613	Fasting lipid values (LDL-C)	24 weeks
P022	Randomised, db, factorial design	MK-0524 A 1g/2g + simvastatin 10/20/40mg MK-0524A 1g/2g Simvastatin 10-20/20-40/40-40mg 1:1:1:1:1:1:1 ratio	1398	Fasting lipid values (LDL-C)	12 weeks
Flushing efficacy studies					
P020	Randomised, db, pc	See above	See above	Max GFSS categorised as none/mild, moderate, severe, extreme after 1 week of treatment	24 weeks
P023	Randomised, db, parallel	MK-0524A run-in → Placebo (5 day drug holiday) → MK-0524A 2g (7 days) → Placebo (5 day drug holiday) → ER-niacin 2g (7 days) → MK0524A 2g	899	Max GFSS categorised as none/mild, moderate, severe, extreme during first 7 days after a 5 day drug holiday	8 weeks run-in 2 weeks treatment
P054	Randomised, db, parallel	MK-0524A 1g (week 0) → 2g (week 4) ER-niacin 0.5g→ 1g→ 1,5g→ 2g (every 4 weeks)	1451	Max GFSS during week 1 # days/week with moderate or greater GFSS (≥ 4) across treatment period	
Safety					
Pooled P011, P015, P026 phase C	b, pc	MK-0524A 2g 221 Placebo 68	289	Safety	1 year
P020, P022 and P054	Randomised, db, pc	MK-0524A 2328 Niacin 1268 Placebo 863	4469	Safety	Up to 24 weeks

Lipid altering effect of laropiprant (study P011)

Information on the effect of laropiprant on lipid parameters was provided. A dose of 150 mg laropiprant did not affect HDL-C and TG, whereas a small (<3% change) was noted in LDL-C. As these levels are known to fluctuate, changes within this limit were not considered relevant.

Dose finding (studies P011 and P033)

The co-administration of laropiprant with nicotinic acid was shown to be effective in reducing flushing symptoms caused by nicotinic acid. No dose-dependency was noted in the daily dose range of 18.75-150 mg laropiprant when 1 g of nicotinic acid was given daily. A dose-dependent response was noted between 5 mg and 37.5 mg when 1 g nicotinic acid was administered. Thus, the pharmacological

effect may still be present at dosages lower than 20 mg. A minimal effective dose has not been established. Less effect is shown at dosages < 37.5 mg laropiprant when added to 2 g dose of nicotinic acid indicating that with the 2 g dose of nicotinic acid there is still dose-dependency effect between 10 mg and 37.5 mg of laropiprant. These observations suggest that as a starting dose, the combination of 20 mg of laropiprant with 1 g of nicotinic acid is suitable, which can be followed by combination of 40 mg laropiprant with 2 g of nicotinic acid (double dose of 20 mg laropiprant/1 g nicotinic acid tablet) in chronic use.

Flushing Symptom Questionnaire validation (study P015)

The Flushing Symptom Questionnaire assesses flushing through patient report in electronic diaries, which included the main scoring method for flushing, Global Flushing Severity Score (GFSS). Overall severity of the flushing experience was expressed as the highest severity during the first week (acute flushing). In the assessment of chronic flushing, the number of days per week with flushing of certain severity was used along with the scores on quality of life, the Global Flushing Bothersome Score (GFBS) and the Global Flushing Sleep Bothersome Score (GFSBS). The evaluation of parameters assessing acute flushing showed significant difference in GFSS in week 1 comparing administration of 1 g nicotinic acid with placebo. With respect to the long term effects, the scoring of only once a day/week (main parameter GFSS) showed small differences of 0.5 and 1.5 days of moderate/severe flushing for placebo and 2 g nicotinic acid, respectively. In addition, no major difference in scoring was seen between the 1 g and 2 g nicotinic acid dose. However, the some of the phase III studies were sensitive enough to demonstrate an increase in flushing with increasing dose of ER nicotinic acid/laropiprant, ER nicotinic acid or NIASPAN™.

- Main studies

The Phase III programme was designed to assess two types of efficacy endpoints: those related to lipid effects and those related to NIF. Lipid endpoints, defined as primary or key secondary endpoints in studies P020-02 and P022-02, aimed to show the efficacy of ER nicotinic acid/laropiprant as a lipid-modifying therapy with beneficial effects on LDL-C, HDL-C and TG values. The flushing endpoints were the primary or key secondary endpoints in studies P020-02, P023-00, and P054-00, which were designed to demonstrate the effect of laropiprant in reduction of NIF focusing on major aspects of nicotinic acid use: during the therapy initiation when high degree of flushing is observed, during chronic maintenance therapy, during return to the therapy after missing doses.

Pivotal phase III studies contributing to the efficacy of ER niacin/laropiprant

Study Number	Study Title	Duration	Study population	
			M	F
P020-02	A Worldwide, Multicenter, Double-Blind, Randomised, Parallel, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of MK-0524A in Patients With Primary Hypercholesterolemia or Mixed Hyperlipidemia	24 weeks	981	632
P022-02	A Multicenter, Randomised, Double-Blind, Factorial Design Study to Evaluate the Lipid – Altering Efficacy and Safety of MK-0524B Combination Tablet in Patients With Primary Hypercholesterolemia or Mixed Hyperlipidemia	12 weeks	615	783
P023-00	A Worldwide, Multicenter, Double-Blind, Randomised, Parallel Study to Evaluate the Efficacy of MK-0524A to Improve Tolerability of Extended Release Niacin	10 weeks	363	531
P054-00	Worldwide, Multicenter, Double-Blind, Parallel Study to Evaluate the Tolerability of MK-0524A versus Niacin Extended-Release	16 weeks	840	615

METHODS

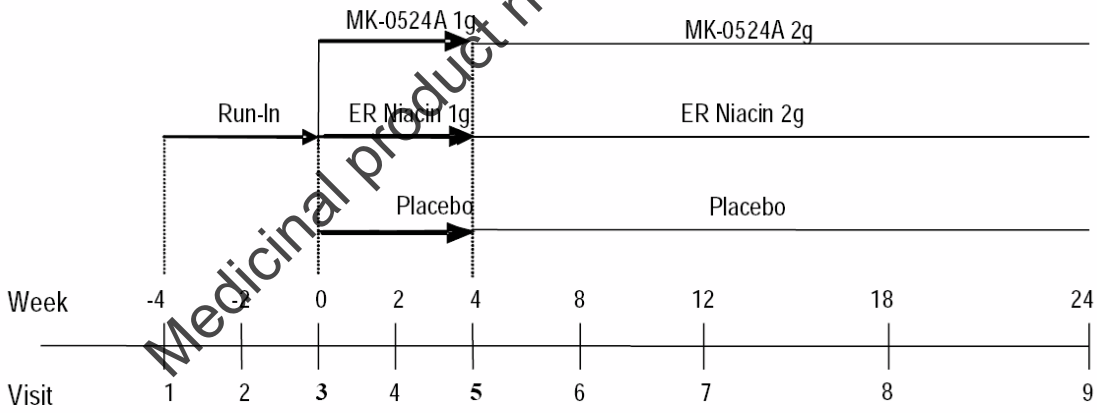
Study Participants

General inclusion/exclusion criteria: Men and women between 18 and about 80 years old with primary hypercholesterolaemia or mixed hyperlipidaemia were included if triglycerides (TG) were ≤350 mg/dL (≤500 mg/dL in protocol P023-00 and P054-00); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were ≤1.5 x the upper limit of normal (ULN); and creatine kinase (CK) was ≤2 x ULN.
Patients with Type I or Type II diabetes mellitus who were poorly controlled, newly diagnosed, had unstable glycemic control, or recent diabetic medication changes were excluded. Patients taking nicotinic acid >50 mg/day, had initiated a lipid-modifying therapy within 6 weeks of visit 1, were concomitantly taking a fibrate and a statin, were women receiving cyclical hormonal contraceptives or intermittently using hormone replacement therapies, taking long-acting NSAIDs, taking aspirin >100 mg per day or on high doses of antioxidant vitamins were excluded. Patients were also excluded in study P020-02 if they were currently experiencing menopausal hot flushes. In P020-02 high risk patients for CHD had to be using a statin, while in P022-02 statin users were excluded. In study P054-00, patients with diabetes mellitus were randomised if glycosylated haemoglobin (HbA1c) was <8%.

Treatments

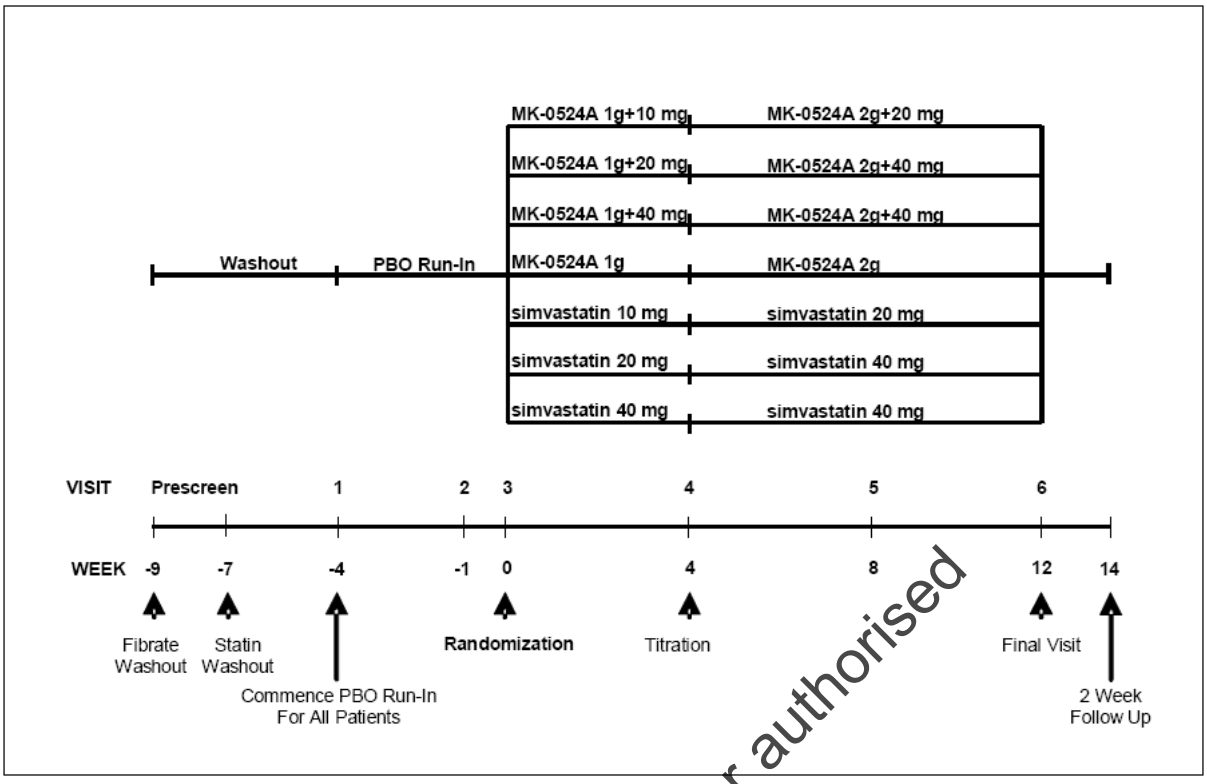
Study P020-02: a bilayer combination tablet consisting of ER nicotinic acid 1 g/laropiprant 20 mg, ER nicotinic acid 1 g alone, or a closely matching double-placebo.
Run-in period (4 weeks): placebo
Treatment period I (4 weeks): 1 tablet in the evening with food
Treatment period II (20 weeks): 2 tablets in the evening with food

Design of study P020-02



Study P022-02: a bilayer combination tablet consisting of ER nicotinic acid 1 g/laropiprant 20 mg. Simvastatin or placebo tablets consisting of simvastatin 10 mg, 20 mg, 40 mg, or a closely matching placebo.
Run-in period (4 weeks): placebo
Treatment period I (4 weeks): 1 tablet of ER nicotinic acid 1 g/laropiprant 20 mg and 1 tablet with a dose of simvastatin in the evening with food
Treatment period II (8 weeks): 2 tablets of ER nicotinic acid 1 g/laropiprant 20 mg and 1 tablet with a dose of simvastatin in the evening with food

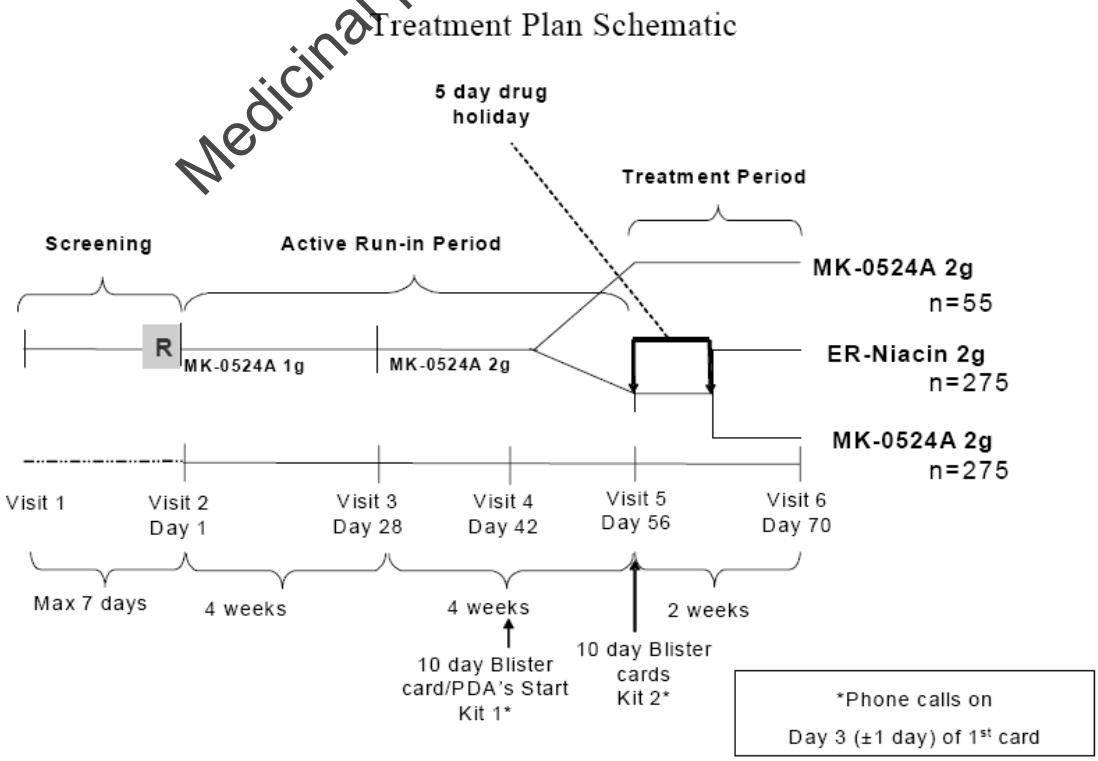
Design of study P022-02



Study P023-00: a bilayer combination tablet consisting of ER nicotinic acid 1 g/laropiprant 20 mg, ER nicotinic acid 1 g alone, or a closely matching placebo
Run-in period: 1 or 2 tablets of ER nicotinic acid 1 g/laropiprant 20 mg in the evening with food
Treatment period:

- Placebo for 5 days (drug holiday) followed by MK-0524A 2 g
- Placebo for 5 days (drug holiday) followed by ER nicotinic acid 2 g
- MK-0524A 2 g

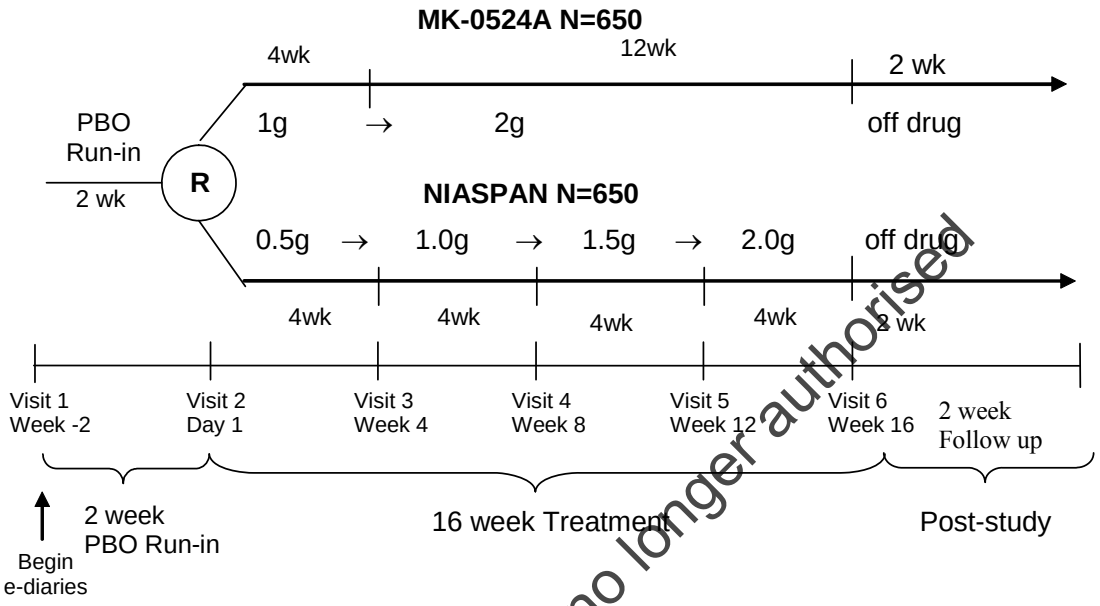
Design of study P023-00



Study P054-00: blinded treatment as ER nicotinic acid 1g/20 mg laropiprant or ER nicotinic acid 0.5 g, 0.75 g, 1 g and matching placebo
Run in period (2 weeks): placebo
Treatment period:

- MK-0524A 1 g increased to 2 g
- Nicotinic acid E-R 0.5 g increased in 0.5 g increments to 2 g

Design of study P054-00



Objectives

P020-02: The primary objective was to evaluate the lipid-lowering efficacy of ER nicotinic acid/laropiprant with or without the use of statins relative to placebo, and its effect on flushing during the acute dosing period relative to ER-nicotinic acid.
Key secondary objectives were effect of ER nicotinic acid/laropiprant on plasma concentrations of HDL-C, TG, LDL-C / HDL-C ratio, non-HDL-C, Apo B, and Apo A-I relative to placebo and the effects on flushing relative to ER-nicotinic acid. Further key secondary objectives were to evaluate the effects in patients not taking concomitant statin therapy and to assess safety and tolerability of ER nicotinic acid/laropiprant.

P022-02: Primary objective was to evaluate LDL-C lowering efficacy of ER nicotinic acid/laropiprant alone or when co-administered with simvastatin compared to ER nicotinic acid/laropiprant in patients with primary hypercholesterolemia or mixed hyperlipidemia.
Key secondary objective was to evaluate the effects of ER nicotinic acid/laropiprant co-administered with simvastatin on HDL-C, TG, LDL-C, LDL-C / HDL-C ratio, non-HDL-C, Apo B, and Apo A-I compared to simvastatin or to ER nicotinic acid/laropiprant, and to assess safety and tolerability of coadministration of ER nicotinic acid/laropiprant with simvastatin.

P023-00: The primary objective was to demonstrate the efficacy of laropiprant in the protection against NIF in patients who resume therapy with either ER nicotinic acid/laropiprant or ER nicotinic acid after a 5-day drug holiday.
The secondary objective was to assess the safety and tolerability of ER nicotinic acid/laropiprant.

P054-00: The primary objective was to assess flushing symptoms with ER nicotinic acid/laropiprant versus ER nicotinic acid in lipid clinic patients for whom nicotinic acid therapy is appropriate.

Key secondary objective was to assess flushing symptoms with ER nicotinic acid/laropiprant versus ER nicotinic acid as measured as GFSS≥4 and to assess the safety and tolerability of ER nicotinic acid/laropiprant versus ER nicotinic acid as measured by the incidence of clinical and laboratory adverse experiences.

Outcomes/endpoints

P020-02: Co-primary endpoints were percent change from baseline across weeks 12-24 in LDL-C and maximum GFSS categorized as none/mild, moderate, severe or extreme during the first week of treatment.
Secondary endpoints were percent change from baseline across weeks 12-24 for HDL-C, TG, LDL-C/HDL-C ratio, non-HDL-C, Apo B, Apo A-I, the number of days with moderate or greater GFSS (GFSS ≥4) during weeks 2-24, the maximum daily GFSS score during week 1, the maximum GFSS categorized as none, mild, moderate, severe, or extreme during week 1, the percentage of patients with maximum GFSS moderate or greater (GFSS ≥4) during week 1, the percent of patients discontinuing study medication due to flushing, the percent of patients with maximum GFSS severe or extreme (GFSS ≥7) during week 1, the number of days per week with mild or greater GFSS (GFSS ≥1) during weeks 2-24, and the percent change from baseline across weeks 12-24 in lipoprotein a (Lp(a)), TC, and TC/HDL-C ratio.

P022-02: The primary endpoint was the percentage change from baseline in LDL-C at week 12.
Key secondary endpoints were percent changes from baseline in HDL-C, TG, LDL-C, LDL/HDL ratio, non-HDL-C, Apo B, and Apo A-1 at week 12. Other secondary endpoints were percent change from baseline in TC, Lp(a), TC/HDL ratio, c-reactive protein (CRP), Apo C-III, and lipid subfractions at week 12. Exploratory endpoints were percent change from baseline in LDL-C, HDL-C, TG, LDL/HDL ratio, non-HDL-C, Apo B, and Apo A-1 at week 4. In addition, repeated measure mixed model analysis was performed using data at weeks 4, 8, and 12 for percent change at week 12 in LDL-C and HDL-C as exploratory sensitivity analyses.

P023-00: The primary endpoint was the maximum GFSS categorized into none/mild, moderate, severe, extreme during the first 7 days following a 5-day drug holiday period.
Secondary Endpoints were maximum GFSS during the first 7 days following a 5-day drug holiday period for percentage of patients with moderate or greater GFSS (GFSS ≥4), and percentage of patients with severe or extreme GFSS (GFSS ≥7), both during the first 7 days following a 5-day drug holiday period.

P054-00: The primary endpoint parameter was the number of days per week with moderate or greater GFSS (GFSS≥4) across the treatment period.
Secondary endpoint parameters were the number of days per week with moderate or greater GFSS (GFSS≥4) across weeks 1, 5, 9, and 13 combined and the number of days per week with moderate or greater GFSS (GFSS≥4) across weeks 2-16. Exploratory endpoint parameters were (1) Percent change form baseline in LDL-C, HDL-C, non-HDL-C, TG, and TC at Week 16; (2) number of days per week with moderate or greater GFSS (GFSS≥4) across Weeks 6-16; (3) number of days per week with severe or extreme GFSS (GFSS≥7) across Weeks 1, 5, 9, and 13 combined; (4) average GFSS score across the treatment period; (5) discontinuing study medication due to flushing (Yes/No); (6) maximum GFSS score across Weeks 1, 5, 9, and 13 combined; (7) maximum GFSS categorized as none/mild, moderate, severe or extreme across Weeks 1, 5, 9, and 13 combined; (8) percentage of patients with maximum GFSS severe or extreme (GFSS≥7) across the treatment period; (9) number of days per week with moderate or greater GFBS during the following time intervals: the treatment period, Weeks 1, 5, 9, and 13 combined, Weeks 2-16, Weeks 6-16; (10) number of days per week with moderate or greater individual symptom scores (itching, tingling, warmth, redness) during the following time intervals: the treatment period, Weeks 1, 5, 9, and 13 combined, Weeks 2-16, Weeks 6-16; (11) median duration of flushing episodes (minutes, as reported on the e-diary) across Weeks 1, 5, 9, and 13 combined; (12) number of days per week with bother score of difficulty sleeping due to flushing (moderate or greater) across Weeks 1, 5, 9, and 13 combined; (13) Flushing Impact Questionnaire variables score(s); (14) number of days per week with aspirin or other NSAID use to

mitigate flushing symptoms during the following time intervals: across the treatment period, across Weeks 1, 5, 9, and 13 combined, across Weeks 2-16, across Weeks 6-16.

With respect to the NIF, the experience is defined as a collection of symptoms including itching, tingling, redness and warmth. Differences can be observed with respect to the number and types of symptoms, experienced during a flushing episode, frequency of flushing episodes in a given treatment period, duration of each episode or the severity of the individual flushing symptoms. All of these factors form the overall patient's flushing experience and its consequent impact on the quality of life. Flushing symptoms were assessed through patient report on electronic diaries using the Flushing Symptom Questionnaire (FSQ) and specifically the Global Flushing Severity Score (GFSS). A family of GFSS-based flushing endpoints was used in each of the studies with flushing endpoints to quantify the number of patients experiencing flushing and their frequency and intensity. Percentage of patients discontinuing therapy due to flushing was also assessed.

Sample size

P020-02: A total of 1613 patients were randomised, 800 on ER nicotinic acid/laropiprant, 543 on ER nicotinic acid and 270 on placebo.

P022-02: A total of 3 302 patients were screened, of which 1 904 were excluded and 1 398 were randomised. Of the 1 398 patients randomised, 1 135 (81.2%) completed the study and 245 (17.5%) patients discontinued study drug prior to the trial completion.

P023-00: In the MK-0524A/Placebo/MK-0524A group 406 patients were randomised and 309 analysed in the All-Patient-Treated analysis. In the MK-0524A/Placebo/ER nicotinic acid group, 411 patients were randomised and 325 analysed in the All-Patient-Treated analysis. In the MK-0524A/MK-0524A group 77 patients were randomised and 57 patients were analysed in the All-Patient-Treated analysis.

P054-00: 726 patients were randomised to MK-0524A and 729 to ER Nicotinic acid, 1 patient in the MK-0524A and 2 patients in the ER Nicotinic acid discontinued prior to treatment.

For all four studies, the sample size and number of patients in each treatment group were considered adequate.

Randomisation

A computer-generated randomisation schedule stratified by centre and presence/absence of concomitant statin medication, if applicable, was used for this study, and patients were randomised and assigned an allocation number *via* interactive voice response system (IVRS).

Blinding (masking)

In all studies, the investigator, site personnel, patients, and research personnel were blinded to treatment assignment during the study period and before the database was complete and clean. Blinding was accomplished by random, masked, assignment of allocation numbers to the treatment groups and by ensuring the drug supplies (active and placebo) administered in the treatment groups appear identical.

Statistical methods

Lipid lowering: study P020-02 and P022-02: An analysis of variance (ANOVA) model was used to analyze the primary lipid endpoint of percent change from baseline in LDL-C across Weeks 12 to 24 and testing the difference in least square means of MK-0524A versus placebo.
Key secondary lipid endpoints of percent change from baseline in HDL-C, LDL-C/HDL-C ratio, non-HDL-C, Apo B, Apo A-I were analysed by the ANOVA model similar to the one used for the LDL-C

analysis. Percent change from baseline in TG was analysed using non-parametric methods based on medians.

GFSS (flushing) efficacy: study P020-02, P023-00 and P054-00: The primary and secondary endpoints used the Cochran-Mantel-Haenszel (CMH) test stratified by country. The primary analysis was performed on the Full Analysis Set (FAS) population, which included all patients who took at least one dose of the treatment study drug and had at least one treatment period GFSS score available. All days with e-diary entries across the treatment period were used to define the primary endpoint.

RESULTS

Participant flow

The following tables show the randomised subject disposition of the phase III pivotal trials.

Study P020-02

	MK-0524A	ER niacin	Placebo	TOTAL
SCREENING FAILURES:				1693
RANDOMIZED:	800	543	270	1613
Male (age range)	475 (21-83)	349 (23-85)	157 (33-84)	981 (21-85)
Female (age range)	325 (27-81)	194 (25-85)	113 (28-83)	632 (25-85)
PRE-TREATMENT	n=2	n=2	n=0	n=4
DISCONTINUED:	2	2	0	4
Clinical Adverse Experience	0	1	0	1
Flushing with Product	1	0	0	1
Other	1	1	0	2
TREATMENT	n=798	n=541	n=270	n=1609
COMPLETED:	570 (71.4%)	347 (64.1%)	239 (88.5%)	1156 (71.8%)
DISCONTINUED:	228 (28.6%)	194 (35.9%)	31 (11.5%)	453 (28.2%)
Clinical adverse experience	68 (8.5%)	36 (6.7%)	12 (4.4%)	116 (7.2%)
Flushing with product	81 (10.2%)	120 (22.2%)	2 (0.7%)	203 (12.6%)
Laboratory adverse experience	16 (2.0%)	3 (0.6%)	1 (0.4%)	20 (1.2%)
Other	63 (7.9%)	35 (6.5%)	16 (5.9%)	114 (7.1%)

Study P022-02

	MK-0524A 2 g+20 and 40 mg (pooled)	MK-0524A 2g	Simvastatin 20 and 40 mg (pooled)	TOTAL
SCREENING FAILURES:				1904
RANDOMIZED:	610	195	593	1398
Male (age range)	265 (26-82)	82 (30-76)	268 (24-83)	615 (24-83)
Female (age range)	345 (24-84)	113 (24-79)	325 (20-85)	783 (20-85)
COMPLETED:	478 (78.4%)	143 (73.3%)	532 (89.7%)	1153 (82.5%)
DISCONTINUED:	132 (21.6%)	52 (26.7%)	61 (10.3%)	245 (17.5%)
Clinical adverse experience	72 (11.8%)	27 (13.8%)	29 (4.9%)	128 (9.2%)
Flushing with product	29 (4.8%)	17 (8.7%)	2 (0.3%)	48 (3.4%)
Laboratory adverse experience	0 (0.0%)	0 (0.0%)	3 (0.5%)	3 (0.2%)
Other	31 (5.1%)	8 (4.1%)	27 (4.6%)	66 (4.7%)

Active Run-in Plus Drug Holiday

	MK-0524A 1g/ MK-0524A 2g/ Placebo
SCREENING FAILURES:	412
RANDOMIZED:	894
Male (age range)	363 (18-80)
Female (age range)	531 (18-80)
COMPLETED:	1
DISCONTINUED:	200
Clinical adverse experience	69
Flushing with product	68
Laboratory adverse experience	8
Other	55

Post-Holiday

	Placebo/ MK-0524A 2 g N=312	Placebo/ ER niacin 2 g N=325	MK-0524A 2g/ MK-0524A 2 g N=57	TOTAL
RANDOMIZED:	312 (19-70)	325 (21-70)	57 (22-71)	694 (19-71)
Male (age range)	190 (19-70)	196 (26-70)	38 (22-71)	424 (19-71)
Female (age range)	122 (27-70)	129 (21-70)	19 (34-68)	270 (21-70)
COMPLETED:	308	324	57	689
DISCONTINUED:	3	1	0	4
Flushing with product	2	1	0	3
Other	1	0	0	1

1 Active Run-In Plus Drug Holiday: Patients took MK-0524A 1 g for 4 weeks, then advanced to MK-0524A 2 g for 4 weeks, followed by Placebo or MK-0524A 2 g (10:1) for 5 days. Post Holiday: On Day 7 after Visit 5, patients took double-blinded study medication, MK-0524A 2 g, or ER niacin 2 g (5:6). 1:6 of the MK-0524A 2 g treated patients had never experienced a drug holiday and are classified by the treatment group MK-0524A 2 g/MK-0524A 2 g.

2 MK-0524A 1g/MK-0524A 2 g/Placebo: MK-0524A 1g for 4 weeks, followed by MK-0524A 2 g for 4 weeks, followed by placebo for 5 days (drug holiday). Placebo/MK-0524A 2 g: MK-0524A 2 g for 7 days following the drug holiday period. Placebo/ER niacin 2 g: ER niacin 2 g for 7 days following the drug holiday period. MK-0524A 2 g/MK-0524A 2 g: MK-0524A 2 g during the 5-day drug holiday (no drug holiday), followed by MK-0524A 2 g for 7 days.

3 One patient is listed as completed for the Active Run-in Plus Drug Holiday phase. This patient was incorrectly phased in the database based on tie-breaker rules. This patient took post-holiday treatment. Therefore, he is also counted in the number of patients who took drug during the post-holiday treatment period (N=312) but not in the number of patients who completed or discontinued during the post-holiday period.

Study P054-00

	MK-0524A	Niacin E-R	TOTAL
SCREENING FAILURES:			569
RANDOMIZED:	726	729	1455
Male (age range)	421 (18-80)	419 (19-80)	840 (18-80)
Female (age range)	305 (21-80)	310 (18-77)	615 (18-80)
PRE-TREATMENT	n=1	n=2	n=3
DISCONTINUED:	1	2	3
Clinical Adverse Experience	0	1	1
Other	1	1	2
TREATMENT	n=725	n=727	n=1452
COMPLETED:	529 (73%)	522 (71.8%)	1051 (72.2%)
DISCONTINUED:	196 (27%)	205 (28.2%)	401 (27.6%)
Clinical adverse experience	70 (9.7%)	53 (7.3%)	123 (8.5%)
Flushing with product	54 (7.4%)	90 (12.4%)	144 (9.9%)
Laboratory adverse experience	11 (1.5%)	5 (0.7%)	16 (1.1%)
Other	61 (8.5%)	57 (8.6%)	118 (8.1%)

Recruitment

Studies were conducted in USA, Canada, Europe, Australia, Asia, Latin America.
P020-02: 16-Jan-2006 to 07-Dec-2006 (138 sites)
P022-02: 17-May-2006 to 14-Jan-2007 (108 sites)
P023-00: 17-Jul-2006 to 19-Jan-2007 (68 sites)
P054-00: 09-Aug-2006 to 14-Mar-2007 (110 sites)

Conduct of the study

In both studies, *P020-02* and *P022-02*, two protocol amendments were implemented. The protocol amendments were not considered to have an influence on the interpretation of the study results. No major protocol deviations have been identified.

P023-00: Changes to the conduct of the study P023-00 were implemented, including the analysis of maximum duration of flushing, which was not pre-planned. The additional analysis was clearly described and was performed prior to unblinding of the data.

P054-00: No formal protocol amendments were declared for the study; however, certain aspects in the analysis of the study results were changed, raising a concern for their potential effect on result evaluation. The nature of the individual changes was clarified. These included addition or deletion of assessment factors, e.g. country, GFFS scores, evaluation of medication discontinuation due to flushing. These were conducted to facilitate the comparison across the studies and to enable the integration of the results across the programme. These analyses have been cited as unplanned in the clinical study report.

Baseline data

P020-02: Elderly patients (≥65 years) accounted for 29.4% of the study population, 66.5% of subjects used statins. The mean baseline LDL-L level was 113.5±40.2 mg/d. Baseline data were considered to be comparable across the treatment groups.

P022-02: Elderly patients (≥65 years) accounted for 25.8% of the study population. The mean baseline LDL-L level was 151.3±16.5 mg/d. Baseline data were considered to be comparable across the treatment groups.

P023-00: Elderly patients (≥65 years) accounted for 15.3% of the study population. The mean baseline LDL-L level was 118.1±37.6 mg/d. Baseline data were considered to be comparable across the treatment groups.

P054-00: Elderly patients (≥65 years) accounted for 25.2% of the study population and 46.5% used statins. The mean baseline LDL-L level was 111.0±39.4 mg/d. Baseline data were considered to be comparable across the treatment groups.

Numbers analysed

The number of patients/treatment arm was adequately reported for each pivotal study including the information on patients who discontinued treatment and did not complete the study protocol. Of the 1613 patients randomized in the study *P020-02*, 1609 received study treatment, and 453 (28.1%) discontinued study drug prior to the trial completion.
More than 80% of the randomised patients in study *P022-02* completed the trial. There was a higher number of patients discontinuing the treatment in the ER nicotinic acid/laropiprant group than in the group taking simvastatin in addition to the combination.
A significant number of discontinuations was noted prior to the post-drug-holiday phase of study *P023-00* (200 out of 894 randomised patients). These were equally distributed across the treatment groups. The primary outcome measure in this study focuses on the post-drug-holiday period, in which the numbers of patients discontinuing treatment were low and thus, this issue does not raise a concern.
In study *P054-00*, approximately 99% randomized patients were included in the full analysis set.

Outcomes and estimation

LIPID LOWERING EFFECTS

Study P020-02
Patients in P020-02 were randomized after a 4 week run-in period to one of the 3 treatment groups (MK-0524A, nicotinic acid or placebo) and after 4 weeks the dose was raised from nicotinic acid 1g to 2g in the MK-0524 and nicotinic acid groups until week 24.

A significantly greater reduction in LDL-C was observed in study P020-02 in the ER nicotinic acid/laropiprant group compared with placebo. The reduction in LDL-C of ER nicotinic acid/laropiprant increased when the dose was increased from 1 g to 2 g nicotinic acid, in week 4, with the slope of reduction diminishing until week 24. Results based on the least square (LS) means (or medians) within each treatment group as well as the differences in LS mean (or medians) between MK-0524A and placebo for the primary and key secondary lipid endpoints are in the table below.

Primary and Key Secondary Lipid Endpoints LS Mean (95% confidence interval (CI) for Percent Change from Baseline across Weeks 12 to 24

Lipids Across Weeks 12 to 24	Entire Study Cohort			Statin Naïve Cohort		
	MK-0524A ($n^{\dagger}$=696)	Placebo ($n^{\dagger}$=257)	Difference vs. Placebo	MK-0524A 2g ($n^{\dagger}$=227)	Placebo ($n^{\dagger}$=85)	Difference vs. Placebo
LDL-C	-18.9 (-21.0, -16.8)	-0.5 (-3.3, 2.4)	-18.4 (-21.4, -15.4)	-20.8 (-24.6, -17.0)	-3.5 (-8.1, 1.2)	-17.4 (-21.5, -13.2)
HDL-C	18.8 (17.2, 20.4)	-1.2 (-3.4, 1.0)	20.0 (17.7, 22.3)	18.8 (15.1, 22.5)	-0.6 (-5.0, 3.9)	19.4 (15.4, 23.3)
Triglycerides (median)	-21.7 (-23.9, -19.5)	3.6 (-0.5, 7.6)	-25.8 (-29.5, -22.1)	-21.8 (-26.2, -17.5)	7.7 (-0.8, 16.2)	-27.8 (-34.9, -20.9)
LDL-C:HDL-C ratio	-28.9 (-31.3, -26.5)	2.3 (-1.0, 5.5)	-31.2 (-34.6, -27.8)	-31.1 (-35.6, -26.6)	-1.1 (-6.6, 4.3)	-30.0 (-34.9, -25.1)
Non HDL-C	-19.0 (-20.8, -17.2)	0.8 (-1.6, 3.3)	-19.8 (-22.4, -17.3)	-20.8 (-24.2, -17.4)	-1.5 (-5.6, 2.6)	-19.3 (-23.0, -15.6)
Apo B	-16.4 (-18.0, -14.7)	2.5 (0.2, 4.7)	-18.8 (-21.2, -16.5)	-18.4 (-21.8, -15.1)	1.2 (-2.9, 5.3)	-19.6 (-23.2, -16.0)
Apo A-1	11.2 (10.1, 12.4)	4.3 (2.7, 5.9)	6.9 (5.3, 8.6)	11.1 (8.6, 13.6)	4.7 (1.7, 7.8)	6.4 (3.7, 9.1)

† Sample size is based on the number of patients included in the analysis of the primary lipid endpoint (percent change from baseline across weeks 12 to 24 in LDL-C).
All comparisons of MK-0524A versus placebo were statistically significant (p<0.001).

P022-02
Patients in P022-02 were randomized after a 5 week washout and 2 week run-in period to MK-0524A 1g + 10 mg, 20 mg or 40 mg simvastatin, MK0524A alone, or simvastatin 10 mg, 20 mg or 40 mg alone. Doses were doubled after 4 weeks, except for the 2 highest dose groups.

This study showed further significant reduction in LDL-C by combining ER nicotinic acid/laropiprant 2g and simvastatin versus ER nicotinic acid/laropiprant 2g or simvastatin alone. A summary of the treatment effects expressed in LS means (or medians) for the primary and key secondary lipid endpoints are in the table below.

Summary of LS Mean (95% CI) for Percent Change from Baseline at Week 12 in the Primary and Key Secondary Lipid Endpoints Full-Analysis-Set

Lipids Endpoints	MK-0524A +Simvastatin ($n^{\dagger}$=520)	MK-0524A ($n^{\dagger}$=160)	Simvastatin ($n^{\dagger}$=565)	MK-0524A+ Simvastatin vs. MK-0524 A	MK-0524A+ Simvastatin vs. Simvastatin
LDL-C	-47.9 (-50.0, -45.8)	-17.0 (-20.3, -13.6)	-37.0 (-39.1, -35.0)	**-30.9 (-34.4, -27.3)**	**-10.8 (-13.2, -8.4)**
HDL-C	27.5 (25.8, 29.2)	23.4 (20.7, 26.2)	6.0 (4.3, 7.6)	4.1 (1.2, 6.9)	**21.5 (19.6, 23.5)**
Triglycerides (TG, median)	-33.3 (-36.1, -30.6)	-21.6 (-27.1, -16.1)	-14.7 (-17.1, -12.3)	-10.8 (-15.4, -6.2)	**-18.7 (-21.6, -15.8)**
Non HDL-C	-45.8 (-47.7, -43.9)	-18.1 (-21.1, -15.0)	-33.4 (-35.3, -31.6)	**-27.7 (-31.0, -24.5)**	-12.4 (-14.6, -10.2)
Apo B	-41.0 (-42.8, -39.1)	-17.1 (-20.2, -14.1)	-28.8 (-30.6, -27.0)	**-23.8 (-27.0, -20.6)**	-12.2 (-14.3, -10.1)
Apo A-I	8.6 (7.1, 10.0)	8.2 (5.9, 10.6)	2.3 (0.9, 3.7)	0.3 (-2.1, 2.8)	**6.3 (4.6, 7.9)**
LDL-C:HDL-C Ratio	-57.1 (-59.4, -54.8)	-31.2 (-34.9, -27.6)	-39.8 (-42.0, -37.6)	-25.9 (-29.8, -22.0)	-17.3 (-19.9, -14.7)

MK-0524A+Simvastatin = MK-0524A 2 g+simvastatin all doses pooled; Simvastatin = simvastatin all doses pooled.
† Sample size is based on the number of patients included in the analysis of the primary lipid endpoint (percent change from baseline at Week 12 with last post-titration (Period II, after Visit 4) value carry forward in LDL-C).

The most important secondary endpoints with respect to the increase of HDL-C and decrease of TG are in accordance with the primary endpoint. In study P020-02, the HDL-C levels increased significantly 20.0 (17.7, 22.3) difference between MK-0524A *vs* placebo, and in study P022-02, with 4.1 (1.2, 6.9) difference between MK-0524A with pooled simvastatin 20 and 40 mg *vs* MK0524A. The levels of TG were significantly reduced.

In summary, both studies showed that the fixed combination of laroprirant and nicotinic acid reduces LDL-C and triglycerides and increase HDL-C. These results are in line with the known characteristics of nicotinic acid. Comparison between laropiprant and nicotinic acid alone indicates that the combination with laropiprant does not affect the effects of nicotinic acid on lipids, in particular the LDL-C lowering effect. This confirms earlier conclusions from the pharmacodynamic studies, especially study P-011. The co-administration of simvastatin showed greater reductions of LDL-C and TG values as well as the increase in HDL-C, in comparison with simvastatin monotherapy.

FLUSHING

P020-02
Study P020-02 was conducted for assessing the effect on the acute flushing (in addition to the assessment of the lipid lowering effects).

Evaluation of the primary endpoint - maximum GFSS categorized as none/mild, moderate, severe or extreme during the first week of treatment – showed that administration of ER nicotinic acid/laropiprant results in a significant less moderate, severe and extreme flushing compared to ER nicotinic acid. Patients taking the combination reported lower number of days per week, on which they experienced moderate to severe flushing (GFSS ≥ 4) in comparison with ER nicotinic acid. This resulted in lower study discontinuation due to flushing (10.2% in MK-0542A group vs 22.2% in ER nicotinic acid group). However, almost no patients discontinued treatment after week 16, which raises the question whether laropiprant is still efficacious after this period. No comparison has been made between patients who stay on ER nicotinic acid/laropiprant and patients who have discontinued treatment with laropiprant. Since flushing declines during long term treatment, the CHMP expressed a concern that the long term efficacy of the combination remains unproven. Therefore, a study demonstrating the impact of long-term withdrawal of laropiprant on flushing symptoms in patients on a stable nicotinic acid maintenance dose will be performed. This has been noted as a Follow up measure in the Letter of undertaking.

Maximum GFSS categorized as None/Mild, Moderate, Severe, Extreme during week full-analysis-set (Study 020-02)

Treatment	None/Mild n (%)	Moderate n (%)	Severe n (%)	Extreme n (%)	Total N
MK-0524A	538 (68.9)	136 (17.4)	80 (10.2)	27 (3.5)	781
ER niacin	233 (44.0)	120 (22.7)	135 (25.5)	41 (7.8)	529
Placebo	246 (93.9)	15 (5.7)	1 (0.4)	0 (0.0)	262

Between-Group Comparison	p-Value†
MK-0524A vs ER niacin	<0.001

† p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.
MK-0524A = MK-0524A 1 g for 4 weeks followed by MK-0524A 2 g for 20 weeks.
ER niacin 2 g = 2 x ER niacin 1 g tablet.

P023-00

Study P023-00 was conducted to determine the effects of a 5 day drug holiday period on acute flushing with ER nicotinic acid 2g/laropiprant 40 mg. Patients underwent a 4 week MK-0524A 1g run-in phase, after which followed 4 weeks with MK-0524A 2g run-in period and then were treated with: 5 day drug holiday + MK0524A 2g; or 5 day drug holiday + ER-nicotinic acid 2g; or stayed on MK-524A 2g for another 2weeks.

All primary and secondary efficacy endpoints were significant in favour of MK-0542A ($p<0.01$ in all tests). The maximum GFSS categorised as none/mild, moderate, severe and extreme during the first 7 days following the 5 day drug holiday was significantly lower in the ER nicotinic acid/laropiprant 2 g arm than in the ER nicotinic acid 2 g arm; the difference in the LS means of maximum GFSS was -0.6 ($p=0.005$). The percentage of patients with moderate GFSS was 29.8% with MK-0542A 2 g and 40.9% with ER nicotinic acid 2g ($p=0.004$). However, only a 10% difference between each group in none/mild category was obtained (non/mild 70.2%, 59.1% and 82.5% for MK-0524A, ER nicotinic acid, and non-drug holiday group, respectively). Reliable discontinuation rates could not be obtained due to the short follow-up time. Nevertheless, considering the significant reduction in severe flushing observed after drug-holiday, results of the study support the proposed posology and no up-titrating from very low doses is needed after this period.

Maximum GFSS Categorized as None/Mild, Moderate, Severe or Extreme During the First Seven days Following a 5-day Drug Holiday Full-Analysis-Set

Treatment	None/Mild n (%)	Moderate n (%)	Severe n (%)	Extreme n (%)	Total N
Placebo/MK-0524A 2 g	217 (70.2)	62 (20.1)	26 (8.4)	4 (1.3)	309
Placebo/ER niacin 2 g	192 (59.1)	80 (24.6)	47 (14.5)	6 (1.8)	325
MK-0524A 2 g/MK-524A 2 g	47 (82.5)	8 (14.0)	1 (1.8)	1 (1.8)	57

Between-Group Comparison	p-Value†
MK-0524A vs. ER niacin following 5-day drug holiday	0.002

† p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.
Placebo/MK-0524A 2 g = 5-day drug holiday followed by 7 days of MK-0524A 2 g.
Placebo/ER niacin 2 g = 5-day drug holiday followed by 7 days of ER niacin 2 g.
MK-0524A 2 g/MK-0524A 2 g = No drug holiday followed by 7 days of MK-0524A 2 g.

P054-00

After a 2 week run-in period, patients were randomized to NIASPAN™ followed by dose titration of nicotinic acid (0.5 g every 4 weeks to final 2 g after 12 weeks) or 4 weeks ER nicotinic acid 1g/laropiprant 20 mg raised after 4 weeks to ER nicotinic acid 2g/laropiprant 40 mg for a total of 16 weeks. The patients on the fixed combination of laropiprant and nicotinic acid were averagely on a higher nicotinic acid-dose that the NIASPAN™ patients.

Evaluated were the number of days per week with moderate or greater GFSS (GFSS≥4) across the treatment period and secondarily, the number of days per week with moderate or greater GFSS (GFSS≥4) across weeks 1, 5, 9, and 13 combined, and the number of days per week with moderate or greater GFSS (GFSS≥4) across weeks 2-16. The exploratory outcomes on quality of life were assessed using the FIQ score (Flushing Impact Questionnaire) with analyses of the irritation/frustration domain, sleep energy domain and social domain.

Number of days per week with maximum GFSS≥4 partitioned into 6 categories across treatment period (full-analysis-set)

Treatment	Number of Days per Week with GFSS ≥ 4						
	0 n (%)	>0 and ≤ 0.5 n (%)	>0.5 and ≤ 1 n (%)	>1 and ≤ 2 n (%)	>2 and ≤ 3 n (%)	>3 n (%)	Total N
MK-0524A	337 (46.7)	204 (28.3)	59 (8.2)	43 (6.0)	28 (3.9)	51 (7.1)	722
Niacin E-R	160 (22.0)	247 (34.0)	121 (16.6)	105 (14.4)	50 (6.9)	44 (6.1)	727

Between-Group Comparison	p-Value†
MK-0524A vs Niacin E-R	<0.001

† p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.
MK-0524A = MK-0524A 1 g for 4 weeks followed by MK-0524A 2 g for 12 weeks.
MK-0524A 1 g = ER niacin 1 g/MK-0524 20 mg combination tablet.
MK-0524A 2 g = 2x ER niacin 1 g/MK-0524 20 mg combination tablet.
Niacin E-R = Niacin E-R 0.5 g for 4 weeks increased every 4 weeks in 0.5 g increments to 2 g for last 4 weeks.
Niacin E-R 1 g = Niacin E-R 0.5 g as 2 tablets each.
Niacin E-R 1.5 g = Niacin E-R 0.75 g as 2 tablets each.
Niacin E-R 2 g = Niacin E-R 1 g as 2 tablets each.

Patients treated with MK-0542A experienced less flushing syndromes compared to ER nicotinic acid group, measured by both, the primary and the secondary endpoints. According to the results, approximately 83% of the group using MK-0524A and approximately 72% of the group using nicotinic acid alone had ≤1 day per week with a maximum GFSS≥4, somewhat questioning the clinical relevance and the need for long term treatment. Number of days per week with GFBS or GFSBS score ≥ 4 followed the pattern of the GFSS score. Quality of life scores supported the primary endpoint, as the FIQ score with analyses of the irritation/frustration domain, sleep energy domain, social domain favouring the use of MK-0524A. Discontinuation due to flushing started to differ at week 8 with ER nicotinic acid/laropiprant already being on the highest dose at week 4 and ER nicotinic acid being at the 1.5 g dose at week 8. At week 16, 7.4% discontinued due to flushing with ER nicotinic acid/laropiprant compared to 12.4% with ER nicotinic acid. However, considering the different dose regimens, overall discontinuation rates were the same between the two treatment groups (27% and 28.2%, respectively) due to other clinical AE (2.4% difference) and laboratory AE (0.8%). Regarding the conclusion that ER nicotinic acid/laropiprant also reduces the amount of aspirin/NSAIDS used to mitigate flushing, this has to be interpreted with caution, since these analyses have not been properly pre-specified and fewer patients used aspirin/NSAIDs in MK-0542A treatment group (11.3%) than in the ER nicotinic acid group (21.6%).

- Analysis performed across trials (pooled analyses and meta-analysis)

Comparisons and analyses of results across the pivotal phase III studies P020-02, P022-02, P023-00 and P054-00 were provided. The proportion of females was greater in P022-02 (>50%) than in the other studies (approximately 40%). The proportion of Hispanic patients was larger, and the proportion of Caucasian patients was smaller in the P054-00 trial than in the other studies. There was a significant number of patients >65 years in each study. As patients in the NCEP high risk category were excluded from P022-02, there was a greater proportion of low risk patients in P022-02 than in P020-02. The proportion of patients with diabetes was similar across studies with the exception of P022-02 from which diabetic patients were excluded. There was a considerable number of patients on concomitant statin use. Concomitant use of statins was higher in P020-02 and the combined extension than in the other studies.
Consistent with the data from the individual studies comparing ER nicotinic acid/laropiprant to the nicotinic acid formulations, the incidence of patients discontinued due to flushing symptoms in the ER nicotinic acid/NIASPAN™ group was significantly higher than in the ER nicotinic acid/laropiprant group. This reduction of NIF with ER nicotinic acid/laropiprant compared to ER nicotinic acid or NIASPAN™ was consistent across the subgroups defined by age, gender, race, and region.
ER nicotinic acid/laropiprant was effective in a wide variety of adult patient populations with primary hypercholesterolemia or mixed dyslipidemia, regardless of race, gender, baseline LDL-C, HDL-C and TG or age, and in special populations, such as diabetics. A modest effect of gender and age was identified. The lipid effects of ER nicotinic acid 2 g/40 mg laropiprant were maintained over 52 weeks of treatment.

- Clinical studies in special populations

No separate clinical studies have been performed in special populations during the phase III programme. Analyses across subpopulations in all phase III studies were provided. Female and male patients as well as the relevant age groups have been appropriately included in the studies. The combination of ER nicotinic acid and laropiprant appears to be effective in a variety of adult populations including subjects with primary hypercholesterolemia, mixed dyslipidemia, regardless of the age, race, gender, baseline LDL-C, HDL-C and TG levels. The modest influence of gender and age is not considered of major clinical significance.

No data on the product's use in children have been provided. Treatment is not recommended in this age group.

- Supportive studies

No supportive studies have been provided.

Clinical safety

Since the applied medicinal product is a fixed-dose combination of ER nicotinic acid and laropiprant, the main focus of the safety analysis is based on the published safety profile of nicotinic acid and potential AEs identified in the presented preclinical and early clinical studies for laropiprant. Further emphasis is laid on the safety evaluation of the co-administration with statins, since ER nicotinic acid/laropiprant is intended for use as monotherapy as well as in coadministration.

Based on the literature data, the most common side effects of nicotinic acid are non-serious tolerability issues related to flushing and gastrointestinal effects. The AE of interest include increases in ALT or AST, increase in fasting serum glucose (FSG) or UA, and skeletal muscle effects. Nicotinic acid has also been associated with clinical hepatotoxicity in rare cases. Nicotinic acid product labelling recommends frequent monitoring of liver function tests. Thus, liver function tests were measured routinely in the current phase II and III studies. Consecutive elevations of AST or ALT of ≥3xULN and hepatitis-related clinical AE were analysed as of special interest.

It has also been previously suggested that the concomitant use of statin and nicotinic acid increases the risk of skeletal muscle rare serious adverse events (SAE). Therefore, muscle safety was extensively monitored in the clinical trials presented. Increases in CK ≥10xULN with or without symptoms were analysed as AEs of special interest. There is little clinical trial evidence that nicotinic acid causes myopathy or rhabdomyolysis on its own, or that it potentiates muscle effects of statins when co-administered.
Since nicotinic acid is known to cause small increases in FSG levels and in HbA1c in patients with diabetes, glycemic status was determined at baseline as normal, impaired, or diabetic. Effect on glucose regulation was assessed by changes in FSG in all patients and changes in HbA1c in diabetics. Clinical and laboratory AEs related to glycemic control, along with the number of cases of new onset diabetes and worsening of diabetes, were analysed as AEs of special interest. Due to the known, nicotinic acid-related gastrointestinal side effects, patients with active peptic ulcer disease within 3 months of randomization were excluded from the study.

The main potential AE for laropiprant based on preclinical studies was the off-target activity on the TP receptor. Activation of the TP receptor has been shown to induce platelet aggregation *in vitro*, thus TP antagonism has the potential to inhibit platelet aggregation. Potential bleeding-related AEs were assessed through the routine monitoring. Prothrombin time was measured in study P020-02 and in the Phase II extension. In addition, the most consistent target organ (identified in mice, rats, and dogs) was the liver. All species studied with laropiprant had indications of changes in the liver at high exposures. Liver changes were characterised and assessed predominantly as increased ALT. In all phase III studies and the long-term safety extensions, effects on liver, especially changes in ALT or AST, were evaluated as AEs of special interest.
The potential for AEs of special interest based on the extensive clinical experience with nicotinic acid and on the preclinical findings for laropiprant have been sufficiently determined and targeted in the safety assessment.

- Patient exposure

Assessment of safety profile was performed in the following ways:
- from the individual pivotal studies P020-02, P022-02 and P054-00,
- from a selection of patients from phase II studies who were on the finalized ER nicotinic acid 2 g/laropiprant 40 mg product for up to 1 year (phase C of the studies P011, P015 and P026),
- from the above mentioned studies pooled (phase III and pooled phase C).

All randomized patients in the different safety population groups who received at least one dose of study drug were included in the safety analyses, summarized and analysed according to the treatment they received. Study P023-00 was not included in the analysis due to unsuitable design.
These pooled data are presented and compared across 3 treatment groups:

1. all patients who were randomized to ER nicotinic acid/laropiprant across the phase III and phase II extensions regardless of other background lipid-modifying therapies (ER nicotinic acid/laropiprant-exposed),
2. patients who took either ER nicotinic acid or NIASPAN™ (ER nicotinic acid/NIASPAN™);
3. patients who were randomized to simvastatin or placebo (simvastatin/placebo), and therefore lacking a general distinction in the use of ER nicotinic acid/laropiprant alone or with a statin.

Overall Disposition of Patients
Pooled Studies 020, 022, 054, Combined Phase C Extensions

	MK-0524A Exposed N=2552	ER Niacin/NIASPAN™ N=1272	Simvastatin/Placebo N=931
Treatment	n=2549 (%)	n=1268 (%)	n=931 (%)
pat. completed *	1904 (74.7)	869 (68.5)	828 (88.9)
pat. discont.	645 (25.3)	399 (31.5)	103 (11.1)
*Includes patients who completed Phase 2 Extension Studies with status of 'Completed Study Extension' and 'Patient Completed'			

For ER nicotinic acid/laropiprant-exposed, 2538 patients dosed for a mean exposure of 115.6 days on drug. For ER nicotinic acid, 541 patients dosed for a mean exposure of 199.9 days on drug. For NIASPAN™, 727 patients dosed for a mean exposure of 90.2 days. 338 patients on placebo were dosed for a mean exposure of 186.3 days and 592 simvastatin patients dosed for a mean exposure of 78.3 days.

For the long-term (1-year) safety extensions (Phase C) evaluation, data from three long-term extensions were pooled to provide 1 year safety data for ER nicotinic acid/laropiprant versus placebo as monotherapy or co-administered with statins and other lipid-modifying agents. Phase B results, which were also pooled for analysis, provide additional long-term safety experience with a higher dose of laropiprant (150 mg) coadministered with NIASPAN™ for up to 11 months.

Overall Disposition of Patients MK-0524A Long Term Safety Pool (Phase C)

	MK-0524A 2g N=221	Placebo N=68
Treatment (EXT 1) Phase C and Post-Study (EXT 1)	n=221 (%)	n=68 (%)
completed study extension*	184 (83.3)	57 (83.8)
pat. discont.	37 (16.7)	11 (16.2)
* Includes those patients that had status of 'Patient Completed'		

A positive bias selection of patients to the safety extension pool has been acknowledged in the long-term safety assessment. When interpreting the data from the long-term extensions it has to be considered that patients agreeing to enter the extension are a selected group of patients who may or may not represent the safety profile of individuals randomized to the same treatments from the outset. Moreover, the number of patients from the phase C extension studies is relatively low. Nevertheless, comparison of phase B and C was discussed in order to give a better overview of long term safety, a higher incidence of gastro-intestinal AEs and discontinuation due to gastro-intestinal problems is reported with higher doses of laropiprant. This confirms that the lower discontinuation rate due to flushing is partly offset by other side effects, in particular the occurrence of gastrointestinal symptoms. No difference in AEs of special interest appears in either study phases.

- Adverse events

The incidence of adverse events and drug-related adverse events was similar between ER nicotinic acid/laropiprant ER nicotinic acid/NIASPAN™ and lower in the simvastatin/placebo group with 62.6%, 63.3% and 46.9% of patients experiencing AEs. The rate of discontinuation due to AE is highest in ER nicotinic acid/NIASPAN™ and lowest in simvastatin/placebo, however, the patients exposed to MK-0524A experienced of the most serious drug related adverse events.

As expected, the number (%) of patients with flushing is reduced when laropiprant is added to nicotinic acid (12.3% *vs* 22.8%). A striking group of adverse events were in the gastro-intestinal

adverse events with a rate higher in ER nicotinic acid/laropiprant group compared with ER nicotinic acid/NIASPAN™ leading to discontinuation.

The most common specific AEs and the most common drug related AEs that occurred more frequently in patients taking ER nicotinic acid/laropiprant or ER nicotinic acid than in placebo patients included diarrhea within the gastrointestinal disorders, paraesthesia within nervous system disorders, pruritus within the skin and subcutaneous tissue disorders, and flushing within the vascular disorders.

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by System Organ Class Pooled Studies 020, 022, 054, Combined Phase C Extensions; All-Patients-As-Treated

	MK-0524A Exposed (N = 2548)		ER Niacin/NIASPAN™ (N = 1268)		Simvastatin/Placebo (N = 931)	
	n	(%)	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	1594	(62.6)	803	(63.3)	437	(46.9)
Patients With No Adverse Experience	954	(37.4)	465	(36.7)	494	(53.1)
Cardiac Disorders	48	(1.9)	29	(2.3)	11	(1.2)
Eye Disorders	48	(1.9)	15	(1.2)	19	(2.0)
Gastrointestinal Disorders	421	(16.5)	148	(11.7)	110	(11.8)
General Disorders And Administration Site Conditions	180	(7.1)	105	(8.3)	44	(4.7)
Infections And Infestations	447	(17.5)	226	(17.8)	155	(16.6)
Injury, Poisoning And Procedural Complications	108	(4.2)	49	(3.9)	41	(4.4)
Metabolism And Nutrition Disorders	50	(2.0)	27	(2.1)	10	(1.1)
Musculoskeletal And Connective Tissue Disorders	246	(9.7)	94	(7.4)	117	(12.6)
Nervous System Disorders	298	(11.7)	149	(11.8)	80	(8.6)
Psychiatric Disorders	74	(2.9)	33	(2.6)	25	(2.7)
Respiratory, Thoracic And Mediastinal Disorders	123	(4.8)	72	(5.7)	47	(5.0)
Skin And Subcutaneous Tissue Disorders	397	(15.6)	201	(15.9)	57	(6.1)
Vascular Disorders	335	(13.1)	294	(23.2)	17	(1.8)
Flushing	313	(12.3)	289	(22.8)	10	(1.1)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

This table was run using a "percent incidence". This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding.

Myalgia was reported with ER nicotinic acid/laropiprant, but the incidence rate was higher in the simvastatin/placebo group. The incidence of diarrhoea, dyspepsia, nausea and vomiting was higher in the ER nicotinic acid/laropiprant group than in the other 2 treatment groups. Gout occurred rarely. Of interest is the observation of a higher incidence overall of gastrointestinal AE in ER nicotinic acid/laropiprant patients compared to ER nicotinic acid/NIASPAN™ and simvastatin/placebo groups. Although the distribution and frequency of the relevant specific AEs do not raise an immediate concern, this issue will be reflected in the Risk management plan.

The findings are in favour of the assumption that laropiprant has an acceptable safety profile and that its addition to nicotinic acid does not alter the safety profile significantly of nicotinic acid. The safety profile of ER nicotinic acid is comparable with that of NIASPAN™.

- Serious adverse event/deaths/other significant events

Deaths

Overall, five deaths occurred during the double-blind treatment periods in the phase III studies; three subjects in P022-02 study and one subject in P054-00 study. One death occurred during the double-blind treatment periods in the phase II extension of P011 study. No deaths were reported for patients participating in the phase I or phase II base studies.

From the patients who died, four (out of 2548 patients=0.2%) were in the ER nicotinic acid/laropiprant group, one (out of 1268 patients=0.1%) was in the ER nicotinic acid group, and one died in an on-going study, for which the treatment assignments were not unblinded at the time of analysis (study

P024). No deaths were drug-related and all appeared to be associated with pre-existing factors, known coronary heart disease (CHD) or CHD-equivalent risk conditions, or were due to suicide (one patient).

Non-fatal serious adverse events
Overall, 115 patients experienced serious non-fatal AEs during the study programme, with ten patients with AEs assessed by the investigators as be possibly, probably or definitely related to study drug: eight patients (0.3%) in the ER nicotinic acid/laropiprant exposed treatment group, one patient (0.1%) in the ER nicotinic acid/NIASPAN™ group and one patient (0.1%) in the simvastatin/placebo treatment pool.

Amongst the ER nicotinic acid/laropiprant patients with drug related non-fatal SAEs, five patients reported drug intolerance, spontaneous abortion, cholecystitis/cholelithiasis, unstable angina/flushing/ presyncope, extreme flushing, respectively, and three patients hypersensitivity reactions. The serious AEs of hypersensitivity and drug intolerance occurred shortly after starting the nicotinic acid 1 g/20 mg laropiprant dose. Other symptoms that were common in at least two of the four patients included urticaria, shortness of breath, vomiting, and loss of consciousness. The AE of acute cholecystitis and cholelithiasis, was considered serious and drug-related to ER nicotinic acid/laropiprant and study therapy was discontinued after 91 days. The AE of presyncope (as a consequence of vasodilatation caused by the study drug) and unstable angina pectoris was probably related to study therapy while flushing was definitely related to study therapy.

In study P022-02, the SAE of transient elevation of liver enzymes leading to acute hepatitis was observed in a patient taking ER nicotinic acid/laropiprant+simvastatin. This was considered by the investigator to be definitely not related to study therapy. One other hepatitis-related AE occurred in phase III study P023-00, but similarly, it was not considered drug-related.

Analysis by System Organ Class revealed no significant differences between the cardiovascular events in patients exposed and not exposed to ER nicotinic acid/laropiprant. In general, in the ER nicotinic acid/laropiprant *vs* ER nicotinic acid/NIASPAN™ group, the incidence of AEs was slightly higher in the group exposed to MK-0524A with vascular disorders (0.4% *vs* 0.0%), infection (0.4% *vs* 0.2%) and general disorders/administration site disorders (0.3 *vs* 0.0%), but not for gastrointestinal disorders (0.2 *vs* 0.4%). Additional data on safety will be obtained from other clinical studies currently ongoing.

Only a small number of SAEs was reported during the use of ER nicotinic acid/laropiprant combination and nicotinic acid alone. A slightly higher number of drug-related SAEs were apparent with the ER nicotinic acid/laropiprant combination compared to nicotinic acid alone and placebo. A causal relationship could be attributed in the case of hypersensitivity reactions, but whether this is due to nicotinic acid or laropiprant remains cannot be established. Less than 2% patients in any treatment pool discontinued study due to an SAE.

Adverse events of special interests
The following AEs were pre-specified as AEs of special interest: AEs related to hepatic functions, muscle, and glycemic control.

Hepatic Safety
Liver function tests (LFTs) were measured routinely in all phase II and III studies and elevations of AST or ALT of >3x ULN and hepatitis-related clinical AE were pre-specified as AEa of special interest. No specific signal from LFTs has been identified with laropiprant used either alone or co-administered with nicotinic acid. There were two reports of hepatitis in the entire ER nicotinic acid/laropiprant development programme, neither of which was considered drug related, both had clear alternate causalities (acute alcohol intoxication and infectious mononucleosis). Incidences of any AEs classified as hepatobiliary disorders were low across all studies, and comparable between the ER nicotinic acid/laropiprant and ER nicotinic acid groups.
Drug-related laboratory AEs of increased liver function tests (ALT and/or AST) occurred at a slightly higher rate with ER nicotinic acid/laropiprant than either of the other 2 treatment groups (ER nicotinic acid/NIASPAN™ and simvastatin/placebo). Similarly, the incidence rate of laboratory AEs of increased ALT and AST that led to discontinuation of therapy was slightly higher with ER nicotinic

acid/laropiprant (0.6% and 0.2%, respectively) compared to 0.2% and 0.1% for the simvastatin/placebo group and none for the ER nicotinic acid/NIASPAN™ group. Of the 25 (22 on the 2g dose) ALT and/or AST ≥3xULN elevations that occurred in the ER nicotinic acid/laropiprant treatment group, 10 were presumed to be drug-related. Most cases resolved upon discontinuation of therapy. The recommendation for LFT monitoring proposed in the SPC is considered adequate. Liver toxicity will be closely monitored in the post-marketing surveillance programme as stated in the Risk management plan.

Muscle-Related Safety

ER nicotinic acid/laropiprant is intended for use alone or with statins, therefore a large proportion of patients treated with ER nicotinic acid/laropiprant in the pivotal phase III and long-term safety extensions were also taking statins. Increase in CK ≥10xULN accompanied by unexplained muscle symptoms as AEs of special interest was monitored, as this is a widely accepted definition of myopathy.

Of 2548 patients on ER nicotinic acid/laropiprant, 62.8% were concomitantly taking statins, 41.9% simvastatin, 12.4% atorvastatin, and 8.5% others. There were no reports of rhabdomyolysis in the pivotal phase III or phase II extension studies; however, MK-0524A exposure did increase the proportion of patients with elevated CK ≥ 10x ULN. The incidence of adverse events related to increased CK was highest in ER nicotinic acid/laropiprant group and lowest in simvastatin/placebo group (2.0% and 0.7%, respectively) and a similar trend was observed for drug-related elevations in CK (1.2% and 0.3%). Two patients in the pooled studies reported myopathy, one in the ER nicotinic acid/laropiprant group and one in the ER nicotinic acid/ NIASPAN™ group. Both cases were associated with unusual levels of physical activity. There was one serious and drug-related event of increased CK (12,780 IU/ml). Patient was not on statins and was hospitalized overnight for hydration and observation. The patient's CK was near normal eight days after discontinuing study medication. No apparent differences between the treatment groups regarding CK elevations could be identified and there were no statistically significant between-group differences in the exposure adjusted event rates. Muscle-related AEs will be monitored in the post-marketing use.

Change in Glycemic Status

Increases of approximately 4 mg/dL in FSG were consistently observed across all phase III and phase II extension studies in patients taking ER nicotinic acid/laropiprant. In study P020-02, patients in the ER nicotinic acid group also had a 4 mg/dL increase in FSG, indicating that the effects on glucose might be mediated by the nicotinic acid component. In diabetic patients, there was the same 4 mg/dL increase at the end of P020-02. There were only small increases in HbA1c (0.1%-0.3%) in diabetic patients treated with ER nicotinic acid/laropiprant, ER nicotinic acid, and NIASPAN™, with similar effects across these treatment groups. Observed effects on blood glucose and HbA1c are comparable reported effects for other immediate release or ER forms of nicotinic acid.

Of the 4258 patients without diabetes at baseline, 16 patients met the criteria for new onset diabetes, 12 (0.5%) in the ER nicotinic acid/laropiprant group, 3 (0.3%) in ER nicotinic acid/NIASPAN™ and 1 (0.1%) in the simvastatin/placebo group. There were no significant differences between groups based on analyses of crude or exposure adjusted rates.

Of the 488 patients with diabetes at baseline, 85 patients met the pre-defined definition of 'worsening of diabetes', 54 (19.9%) in the ER nicotinic acid/laropiprant group, 29 (16.7%) in the ER nicotinic acid/NIASPAN™ group and 2 (4.6%) in simvastatin/placebo group.

The data do not raise a specific concern beside the known nicotinic acid effects. Diabetic or potentially diabetic patients treated with ER nicotinic acid/laropiprant should be observed closely as adjustment of diet or hypoglycemic therapy may be necessary.

- Laboratory findings

The incidence rates of laboratory drug events and drug-related laboratory events were comparable between the ER nicotinic acid/laropiprant and nicotinic acid/NIASPAN™ group with the lowest incidence in the simvastatin/placebo group. The proportion of patients who discontinued due to laboratory adverse experiences was highest with ER nicotinic acid/laropiprant (1.3%), compared to ER nicotinic acid/NIASPAN™ (0.7%) and simvastatin/placebo (0.4%). The incidence of drug-related laboratory adverse experiences leading to discontinuation was highest with ER nicotinic

acid/laropiprant (1.1%), followed by ER nicotinic acid/NIASPAN™ (0.4%) and simvastatin/placebo groups (0.2%).

Specific laboratory AE by test category were assessed in pooled treatment groups. Not all tests were performed in all studies. The incidence of laboratory AEs was highest in the Blood Chemistry Test category, with similar incidence rates between the ER nicotinic acid/laropiprant and ER nicotinic acid/NIASPAN™ pools, compared to a lower incidence in the simvastatin/placebo pool. The AE occurring with the highest incidence in this category were increased ALT, AST, blood uric acid, CK, and FSG.

In summary, the evaluation of laboratory AEs of special interest revealed that ER nicotinic acid/laropiprant group had the highest incidence rates, but the absolute numbers were low and no specific laboratory AE emerged. The ER nicotinic acid/laropiprant group had the highest rate of elevated CK levels ≥ 10x ULN, but incidence was very low and absolute conclusions cannot be drawn. Difference in clinical events is not apparent because rates of myopathy and rhabdomyolysis are low. Exposure to laropiprant did not significantly affect glucose levels, whereas the data confirmed that a slight increase may occur after nicotinic acid. Platelet count and prothrombin time were not affected, but laropiprant may affect bleeding time at higher concentrations, however, a potential risk is not apparent from the phase II studies. Therefore, bleeding incidences will be followed up in the PSUR cycles.

- Safety in special populations

A slightly higher percentage of older patients in the ER nicotinic acid/laropiprant and simvastatin/placebo groups reported AEs and/or discontinued treatment due to the AEs. A slightly higher percentage of female than male across all treatment groups reported and discontinued due to AEs. Small differences are present between races, but do not give any reason to exclude a population from treatment with the product.
Patients with impaired renal function (creatinine ≥2 mg/dL) or nephrotic syndrome were excluded from Phase II and III clinical trials. Therefore, no data were provided and this is adequately reflected in the SPC.
The safety and efficacy of the ER nicotinic acid/laropiprant tablet has not been studied in patients with hepatic insufficiency. Patients with chronic hepatobiliary or hepatic disease were excluded from all Phase II and III studies. As with other nicotinic acid products, ER nicotinic acid/laropiprant is contraindicated in patients with significant or unexplained hepatic dysfunction. This is adequately reflected in the SPC.

- Safety related to drug-drug interactions and other interactions

In clinical studies, laropiprant did not significantly alter the pharmacokinetics of midazolam, simvastatin, warfarin, digoxin, oral contraceptives or rosiglitazone providing further in vivo evidence for a low propensity for perpetrating drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and human p-glycoprotein. Multiple doses of laropiprant increased the plasma concentration of a metabolite of midazolam, 1-hydroxymidazolam. These results suggest that laropiprant might be an inhibitor of UGT2B4 and UGT2B7 *in vitro* and that there may be interactions with compounds that are predominantly metabolized by UGT2B4 or UGT2B7. Laropiprant concentrations are not meaningfully altered by clarithromycin suggesting that strong inhibitors of CYP3A4 do not alter laropiprant pharmacokinetics.

No specific evaluation of safety related to drug-drug interactions and other interactions has been provided. However, general pharmacokinetic drug-drug interactions have been extensively investigated and possible mechanisms of interaction discussed. In addition, these issues are adequately reflected in the proposed SPC.

Nevertheless, regarding statins, only investigations on pharmacokinetic interactions between ER nicotinic acid/laropiprant and simvastatin were provided, while specific information on atorvastatin, fluvastatin, pravastatin and rosuvastatin is missing. Subsequently, clinical and laboratory adverse

experience summaries for patients receiving simvastatin 80 mg, atorvastatin 80 mg, and rosuvastatin 40 or 80 mg were provided. There were no ≥3xULN increases in ALT/AST or ≥10xULN increases in CK among patients taking simvastatin 80 mg, atorvastatin 80 mg, or rosuvastatin 40 or 80 mg. However, the results should be viewed with caution due to the relatively small number of patients in each of the statin subgroups. The incidence of clinical and laboratory adverse experiences and discontinuations was comparable for patients in the ER nicotinic acid/laropiprant, ER nicotinic acid /NIASPAN™, and simvastatin/placebo groups, who were also taking 80 mg of simvastatin or atorvastatin. Patients taking rosuvastatin showed the highest incidence of laboratory AE, followed by patients taking lovastatin. More patients taking rosuvastatin discontinued due to laboratory AEs (6.6%) than did patients taking any other statin including simvastatin (1.4%) and atorvastatin (1.0%). The clinical and laboratory adverse experience summaries for patients in the highest dose statin groups was similar in the other statin group compared to the 80 mg simvastatin or atorvastatin group. Additional safety data from patients taking ER nicotinic acid/laropiprant with rosuvastatin will be provided based on new long term clinical trials with patients administered rosuvastatin and ER nicotinic acid/laropiprant.

- Discontinuation due to adverse events

Two primary reasons for discontinuation in both ER nicotinic acid/laropiprant and ER nicotinic acid were flushing symptoms associated with the test product (7.2% and 16.6%, respectively) and clinical AEs (9.7% and 7.0%, respectively). It is apparent that flushing is an important factor for discontinuation, favouring the use of ER nicotinic acid/laropiprant compared to nicotinic acid alone (4.5% *vs* 8.8%).

The lower discontinuation rate due to flushing in the nicotinic acid/laropiprant group in comparison with the nicotinic acid group is partly compensated by the occurrence of AEs related to laropiprant, in particular gastrointestinal AEs (2.5% *vs* 1.5%) and laboratory AEs (1.3% *vs* 0.7%), although the overall incidence is low. The distribution and frequency of the relevant specific AEs do not raise an immediate concern, and most of these effects are accounted for in the Risk management plan.

- Post marketing experience

There is currently no post-marketing experience with the use of this fixed dose combination.

2.5 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 MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Abnormal liver function tests	Routine pharmacovigilance Monitor reports of abnormal liver function tests in ongoing and planned clinical trials	Labelling – EU SPC **4.2 Posology and method of administration** *Use in patients with **hepatic** or renal insufficiency*

		Use of Tredaptive in patients with **hepatic** or renal insufficiency has not been studied. Like other nicotinic acid medicinal products, Tredaptive is contraindicated in patients with significant or unexplained hepatic dysfunction. **4.3 Contraindications** Significant or unexplained hepatic dysfunction. **4.4 Special warnings and precautions for use** *Hepatic effects* Switching from immediate-release (crystalline) nicotinic acid to Tredaptive has not been studied. However, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have switched from immediate-release nicotinic acid to long-acting nicotinic acid at equivalent doses. Therefore, patients switching from immediate-release nicotinic acid to Tredaptive should be initiated at the 1000 mg/20 mg dose. Tredaptive should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Like other lipid-lowering therapies, nicotinic acid medicinal products have been associated with abnormal liver function tests (see section 4.8). Transaminase elevations were reversible upon discontinuation of therapy. Liver function tests are recommended before initiation, every 6 to 12 weeks for the first year, and periodically (e.g. semi-annually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of ≥3 X ULN persist, reduction of dose or withdrawal of Tredaptive is recommended. *Further* As with other nicotinic acid medicinal products, patients with a history of **jaundice, hepato-biliary disorder** or peptic ulcer should be observed closely **4.8 Undesirable effects** *Overall adverse reactions with Tredaptive* Investigations:

		Elevations in ALT and/or AST (consecutive, ≥3 X ULN) *Common.* Total bilirubin *Uncommon* *Investigations* Marked and persistent increases of serum transaminases have been reported infrequently. In controlled clinical studies, the incidence of clinically important elevations in serum transaminases (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 X ULN, consecutive) was 1.0 % for patients treated with Tredaptive with or without a statin. These elevations were generally asymptomatic and returned to baseline after discontinuation of therapy or with continued treatment. Other abnormal laboratory values reported were elevations in LDH, fasting glucose, uric acid, **total bilirubin**, and amylase, and reductions in phosphorus and platelet counts *Nicotinic acid-related adverse reactions* *Hepatobiliary disorders:* Jaundice
Myopathy/rhabdomyolysis in combination with an HMG CoA reductase inhibitor	Routine pharmacovigilance Monitor reports of Myopathy/rhabdomyolysis in combination with an HMG CoA reductase inhibitor in ongoing and planned clinical trials	Labeling - EU SPC **4.4 Special warnings and precautions for use** When Tredaptive is co-administered with a statin, please refer to the Summary of Product Characteristics for that particular medicinal product. *Effect on skeletal muscle* Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1000 mg/day) of nicotinic acid and HMG-CoA reductase inhibitors (statins) Physicians contemplating combined therapy with statins and Tredaptive should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased. Periodic serum CK should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Caution should be exercised in patients with pre-disposing factors for

		rhabdomyolysis. • Age >70 years • Renal impairment • Uncontrolled hypothyroidism • Personal or familial history of hereditary muscular disorders • Previous history of muscular toxicity with a statin or fibrate • Alcohol abuse. If muscle pain, weakness or cramps occur while a patient is receiving Tredaptive with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 x ULN), treatment should be stopped. **4.5 Interaction with other medicinal products and other forms of interaction** *HMG-CoA reductase inhibitors:* When simvastatin is combined with nicotinic acid, a modest increase in AUC and C_{max} of simvastatin acid (the active form of simvastatin) was observed, which may be devoid of clinical relevance. The pharmacokinetic interaction of Tredaptive with statins has been studied only with simvastatin. **4.8 Undesirable effects** *Overall adverse reactions with Tredaptive* Investigations: Elevations in CK (≥10 X ULN) *Uncommon* Clinically important elevations of CK (≥10 X ULN) were seen in 0.3 % of the patients treated with Tredaptive with or without a statin. *Nicotinic acid-related adverse reactions* *Musculoskeletal and connective tissue disorders:* Muscular weakness, **myalgia.**
Impaired glucose tolerance	Routine pharmacovigilance Monitor reports of impaired glucose tolerance in ongoing and planned clinical trials	Labelling – EU SPC **4.4 Special warnings and precautions for use** *Effect on glucose* Nicotinic acid medicinal products have been associated with increases of fasting blood glucose levels. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycaemic therapy may be necessary. **4.8 Undesirable effects**

		<u>*Overall adverse reactions with Tredaptive*</u> Investigations: Elevations in fasting glucose *Common* Other abnormal laboratory values reported were elevations in LDH, **fasting glucose**, uric acid, total bilirubin, and amylase, and reductions in phosphorus and platelet counts As with other nicotinic acid medicinal products, elevations in **fasting glucose** (a median increase of approximately 4 mg/dL), and uric acid (mean change from baseline of +14.7 %), and reductions in platelet counts (a mean change from baseline of -14.0 %) were reported in controlled clinical studies with Tredaptive (2000 mg/40 mg). In **diabetic** patients a median increase in HbA1c of 0.2 % was observed (where modification of hypoglycaemic therapy was allowed). <u>*Nicotinic acid-related adverse reactions*</u> *Metabolism and nutrition disorders:* Impaired glucose tolerance
<u>Important Missing Information</u> Use during pregnancy and lactation	Routine pharmacovigilance Pregnancy registry (US based) The final protocol for the US based pregnancy registry will be included in an updated RMP to be provided by August 2008.	Labelling – EU SPC **4.6 Pregnancy and lactation** <u>*Pregnancy*</u> *Tredaptive* There are no data from the combined use of nicotinic acid and laropiprant in pregnant women. The combination has not been tested in reproductive toxicity studies. The potential risk for humans is unknown. Therefore, Tredaptive should not be used during pregnancy unless clearly necessary. *Nicotinic acid* There are no adequate data from the use of high dose nicotinic acid in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. *Laropiprant* There are no data from the use of laropiprant in pregnant women. Studies in animals have shown reproductive toxicity at high doses of laropiprant. <u>*Lactation*</u> *Tredaptive* No studies in lactating animals have been conducted with Tredaptive. A decision on

		whether to continue/discontinue breast-feeding or to continue/discontinue therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of Tredaptive to the woman. *Nicotinic acid* Nicotinic acid is excreted in human breast milk. *Laropiprant* It is unknown whether laropiprant is excreted in human breast milk. Animal studies have shown excretion of laropiprant in milk.
Use in patients below 18 years of age	Routine pharmacovigilance Monitor reports of use in patients below 18 years of age in ongoing and planned clinical trials including a paediatric study (P071)	Labelling – EU SPC **4.2 Posology and method of administration** *Use in paediatric patients* Safety and effectiveness of Tredaptive in paediatric patients have not been established. Therefore, treatment is not recommended in this age group.
Use in patients greater than or equal to 65 years of age	Routine pharmacovigilance Monitor reports of use in patients greater than or equal to 65 years of age in ongoing and planned clinical trials including HPS2-THRIVE	Labelling as proposed is adequate *Use in the elderly* No dose adjustment is required for elderly patients
Long term exposure (greater than 12 months)	Routine Pharmacovigilance Monitor reports of long term exposure (greater than 12 months) in ongoing and planned clinical trials including long-term safety data from HPS2-THRIVE	The actions described in the pharmacovigilance plan are deemed appropriate to gather additional information concerning use of ER niacin/laropiprant in patients with long term exposure (greater than 12 months). These include routine pharmacovigilance and monitoring reports of patients on long term therapy exposure (greater than 12 months) in ongoing and planned clinical trials including long term safety data from HPS2-THRIVE. Therefore, no specific long term exposure labeling language is deemed required at this time. The Applicant will periodically assess whether product labeling needs to be modified
Concomitant therapy with lipid lowering drugs other than statins	Routine pharmacovigilance	Labelling – EU SPC **4.2 Posology and method of administration** *Concomitant therapy* Because co-administration of bile acid

		sequestrants may reduce the bioavailability of acidic medicinal products such as nicotinic acid, it is recommended that Tredaptive be administered >1 hour before or >4 hours after administration of a bile acid sequestrant. **4.5 Interaction with other medicinal products and other forms of interaction** <u>Effects of other medicinal products on nicotinic acid</u> *Bile acid sequestrants:* Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as nicotinic acid, it is recommended that Tredaptive be administered >1 hour before or >4 hours after administration of a bile acid sequestrant.
Patients on long term therapy exposure - Effects on Platelet Reactivity (Inhibition) - bleeding events	Routine pharmacovigilance Monitor reports of patients on long term therapy exposure - Effects on Platelet Reactivity (Inhibition)- bleeding events in ongoing and planned clinical trials including long-term safety data from HPS2-THRIVE	The actions described in the pharmacovigilance plan are deemed appropriate to gather additional information concerning use of ER niacin/laropiprant in patients with long term exposure -Effects on Platelet Reactivity (Inhibition) - bleeding events. These include routine pharmacovigilance and monitoring reports of patients on long term therapy exposure- Effects on Platelet Reactivity (Inhibition)- bleeding events in ongoing and planned clinical trials including long-term safety data from HPS2-THRIVE. Therefore, no specific long term exposure labeling language is deemed required at this time. The Applicant will periodically assess whether product labeling needs to be modified.
Patients on long term therapy exposure - Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events.	Routine pharmacovigilance Monitor reports of patients on long term therapy exposure - Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events in ongoing and planned clinical trials including long-term safety data from HPS2-THRIVE	The actions described in the pharmacovigilance plan are deemed appropriate to gather additional information concerning use of ER niacin/laropiprant in patients with long term exposure -Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events. These include routine pharmacovigilance and monitoring reports of patients on long term therapy exposure- Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events in ongoing and planned clinical trials including long-term safety data from HPS2-THRIVE. Therefore, no specific long term exposure labeling language is deemed required at this time. The Applicant will periodically assess

		whether product labeling needs to be modified.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substances and medicinal product have been adequately described. Excipients used in the formulation of the medicinal product and the manufacturing process selected are typical for tablet formulations. The results of the tests indicate that the active substance and the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

Non-clinical pharmacology and toxicology

The pharmacodynamic properties of nicotinic acid have been investigated previously and confirm its lipid lowering effects observed in clinical environment. The flushing effect of nicotinic acid is believed to be mediated by the compound's ability to induce the generation of PGD_2, which following its interaction with DP_1 receptors results in vasodilatation observed as undesirable effect of flushing.

The primary pharmacodynamic studies conducted with laropiprant provided adequate evidence that the drug is a high affinity antagonist of DP_1 receptors and exerts an antagonistic action with weaker affinity at the thromboxane A_2 receptor (TP). Laropiprant antagonises the vasodilatory effect of nicotinic acid *via* inhibitory action on DP_1. The oxidative metabolites of laropiprant show markedly lower affinities and potencies at the DP_1 and TP receptors, which are unlikely to contribute to the clinical effects.

The pharmacokinetic investigations of laropiprant showed that absorption after the oral administration to dogs and rats is rapid and the drug is distributed mainly in the gastrointestinal system. Plasma protein binding is >99% in most investigated species. Laropiprant is metabolised *via* oxidation and glucuronidation, with the acyl glucuronide being the major metabolite. The potential interactions between nicotinic acid and laropiprant investigated in toxicokinetis studies in rats did not show any clinical relevance in humans. Laropiprant is excreted mainly *via* faeces and urine.

Low oral toxicity of laropiprant and nicotinic acid was seen in single dose toxicity studies in mice and rats. The repeat dose toxicity studies in mice and other species showed treatment-related effects on liver at all doses. Further evaluation of the potential hepatic adverse effects was investigated in the clinical programme and relevant statements were included in the SPC. Based on the genotoxixity tests performed with laropiprant and on the experience from the long term use of nicotinic acid, both are considered to be void of genotoxic potential. Carcinogenicity studies conducted in rats and mice confirmed that there is no safety concern for humans. Laropiprant was tested in a reproductive toxicity studies in rats and rabbits and there was no indication of a risk for human safety.

The environmental risk of laropiprant was assessed and there is no indication of a risk for bioaccumulation. However, the CHMP considered the method used to determine log K_{OC} as insufficient and a the company committed to conducting additional tests to estimate Koc of laropiprant in soil.

Efficacy

Studies confirm that the fixed combination of laropiprant and ER nicotinic acid reduces LDL-C and triglycerides and increases HDL-C values. These results are in line with the known characteristics of nicotinic acid. Furthermore, the ER nicotinic acid/laropiprant combination produced significant lipid-altering efficacy relative to placebo. ER nicotinic acid/laropiprant co-administered with simvastatin was more effective than either of the individual components with respect to altering levels of LDL-C, HDL-C, and TG without inducing deleterious effects on other lipid parameters. ER nicotinic acid/laropiprant was effective in a variety of adult patient populations with primary hypercholesterolaemia or mixed dyslipidaemia, regardless of race, gender, baseline LDL-C, HDL-C and TG or age and in special populations such as diabetics. The across trial analyses show that the lipid effects were maintained over 52 weeks of treatment in the extensions phase population.

Considering the second primary endpoint, the effect of the ER nicotinic acid/laropiprant on nicotinic acid induced flushing, reduction of these symptoms was achieved by addition of laropiprant to nicotinic acid. A dose-dependent response was noted between 5 mg and 37.5 mg when 1 g nicotinic acid was given daily, but not in the higher dose ranges (up to 150 mg laropiprant). With 2 g nicotinic acid, the dose-dependency was observed in the range 10 mg-37.5 mg laropiprant. A minimal effective dose has not been established, but the pharmacological effect may still be present at doses lower than 20 mg. Thus, the combination of 20 mg laropiprant and 1 g nicotinic acid has been chosen as the initiation dosage. The dosage can be doubled if indicated.

The results of the clinical programme of four pivotal studies indicated that ER nicotinic acid/laropiprant shows less flushing in the acute phase than the monotherapy with nicotinic acid. Important evaluation factor is the number of patients free of flushing and the contribution of flushing to therapy discontinuation. On both primary and secondary endpoints, fewer days with moderate to severe flushing were experienced with the fixed combination than with nicotinic acid monotherapy. The combination product was also effective in the chronic phase and fewer patients discontinued the treatment due to flushing. Reduction in severe flushing was observed after a period of temporary discontinuation of therapy, suggesting no need for up-titrating from very low doses. The effect of long-term withdrawal of laropiprant on flushing symptoms in patients continuing nicotinic acid is under investigation.

Safety

As expected, the number (%) of patients reporting flushing-related AEs is smaller when laropiprant is added to nicotinic acid. One of the main safety issues is whether the addition of laropiprant in this fixed combination leads to an increase in the number and severity of other AEs that might already be associated with nicotinic acid. Of significance are the gastrointestinal AEs showing a higher incidence rate in the ER nicotinic acid/laropiprant group than in the ER nicotinic acid/NIASPAN™ group. However, the majority of these events were non-serious. Incidence of AEs related increased liver function tests was higher with ER nicotinic acid/laropiprant and the product is therefore contraindicated in patients with liver function disorders. In addition, a follow-up requirement regarding liver tests monitoring is included in the Risk management plan.

Only a small number of SAE were reported. A slightly higher number of drug-related SAEs were apparent with the ER nicotinic acid/laropiprant combination compared to nicotinic acid alone and placebo. A causal relationship could be attributed in the case of hypersensitivity reactions, but whether this is due to nicotinic acid or laropiprant remains could not be established. These data originate from a small population of patients and results of the ongoing clinical trial will be reported to the CHMP.

No specific laboratory AE emerged. Any differences in the observed incidence rates result from differences in dose regimen. Safety related to drug-drug interactions is adequately reflected in the SPC.

With regards to the skeletal and muscle related safety, exposure is not sufficient to come to a definite conclusion due to the low occurrence of this AE. The limited data indicate that there is no specific

increase in muscle related AEs for the fixed dose combination. Nevertheless, there is a requirement to specifically monitor muscle related AEs during post marketing surveillance.

Exposure to laropiprant did not significantly affect glucose levels, whereas the data confirmed that a slight increase may occur after nicotinic acid administration. Diabetic or potentially diabetic patients treated with ER nicotinic acid/laropiprant should be observed closely as adjustment of diet or hypoglycaemic therapy may be necessary.

Elderly patients showed higher incidence of AEs and higher discontinuation rate due to AEs, but differences between the treatment arms are small and no specific dose recommendations are necessary. The minor differences between races and between genders do not give any reason to exclude a population from treatment with the product.

In principle, no specific and significant safety issues have been identified in the clinical studies. Furthermore, outstanding issues will be addressed in the ongoing studies with high number of patients. Data related to hepatic, muscle, or bleeding safety profile of the combination product will be evaluated on a large scale.

The findings are in favour of the assumption that laropiprant has an acceptable safety profile and its addition to nicotinic acid does not significantly alter the safety profile of nicotinic acid. It is concluded that the improved tolerability of nicotinic acid/laropiprant combination leading to an enhanced treatment and dosage compliance without compromising the established nicotinic acid effects has been successfully demonstrated. As a commitment, a study will be performed demonstrating the impact on flushing symptoms of long-term withdrawal of laropiprant in patients on a stable nicotinic acid maintenance dose to establish the need for the continued laropiprant use. The risk/balance ration is considered acceptable providing the post-authorisation commitments are fulfilled.

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

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 concerns.

- User consultation

The Applicant performed a user consultation testing on the package leaflet. The results demonstrated that participants of the study were able to find and understand key safety messages. In conclusion, the package leaflet meets the requirements set for user testing.

Risk-benefit assessment

The main benefit of this fixed dose combination therapy was demonstrated when evaluation of nicotinic acid induced flushing in the acute phase (week 1), chronic phase (week 2 and longer) and after a temporary treatment discontinuation showed that the addition of laropiprant to nicotinic acid can be considered effective in reducing the occurrence and severity of flushing symptoms. This is also reflected in the lower flushing related discontinued rates in the combination product group.

The need for a long-term nicotinic acid treatment alternative in form of a fixed dose combination containing laropiprant to reduce flushing seems justified, since nicotinic acid is a life-time treatment. The impact of long-term withdrawal of laropiprant in patients continuing treatment with nicotinic acid on the flushing symptoms was not adequately demonstrated. Therefore, as a follow-up measure, the CHMP requested a commitment to further investigate whether withdrawal of laropiprant after 12-24 weeks of therapy has a negative impact potentially leads to further nicotinic acid treatment discontinuation due to flushing. Until then, the SPC states that efficacy has not been established for period of treatment longer than 24 weeks.

No major safety risks can be attributed to the addition of laropiprant to nicotinic acid on the basis of the clinical data submitted. Gastrointestinal adverse events may occur more frequently, as well as increased liver enzymes and creatinine values, but the causal relationship was not proven. The current experience with the use of this fixed dose combination is limited and will be closely monitored during the post-marketing phase.

The risk-benefit ratio for the fixed dose combination of nicotinic acid/laropiprant was considered favourable, provided the company performs the post authorisation follow up measures and reports to the CHMP within the foreseen timeframes.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Tredaptive in the treatment of dyslipidaemia, particularly in patients with combined mixed dyslipidaemia (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) was favourable and therefore recommended the granting of the marketing authorisation.