27 June 2013
EMA/CHMP/308856/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cholib

International non-proprietary name: fenofibrate / simvastatine

Procedure No. EMEA/H/C/002559/0000

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

LIST OF ABBREVIATIONS

ACCORD (study)	Action to Control Cardiovascular Risk in Diabetes
ACO	Acyl-CoA oxidase
ACS	Acute Coronary Syndrome
ApoB	apolipoprotein B
ATP III	Adult Treatment Panel III
AUC	Area under Curve
BE	Bioequivalence
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence interval
Cmax	Maximal concentration
CRP	C-Reactive Protein
CV	Cardiovascular
CVD	Cardiovascular Disease
CYP	Cytochrome P
DEHP	di(2-ethylhexyl) phthalate
eGFR	Estimated Glomerular Filtration Rate
FA	Fenofibric acid
FDC	Fixed Dose Combination
FIELD (study)	Fenofibrate Intervention and Event Lowering in Diabetes
FXR	Farnesoid X Receptor
GI	Gastro intestinal
HDL-C	High-density lipoprotein cholesterol
HMGCoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
HR	Hazard Ratio
LDL-C	Low-density lipoprotein cholesterol
LLOQ	Lower Limit of Quantification
Lp(a)	Lipoprotein (a)
LXR	Liver X Receptor
MI	Myocardial Infarction
NCEP	National Cholesterol Education Program
PPAR	Peroxysome proliferator activated receptor
PK	Pharmacokinetic
PTY	Patient Treatment Year(s)
SVA	Simvastatin acid
SV	Simvastatin
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
Tmax	Time to peak concentration
TSH	Thyroid Stimulating Hormone
Total-C	Total Cholesterol

UCP	Uncoupling Protein
UGT	UDP-Glucuronosyltransferase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Abbott Healthcare Products Ltd. submitted on 21 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cholib (originally under the name Treakol), through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

Treakol is indicated in adults as adjunctive therapy to diet and exercise in mixed dyslipidaemia where use of a combination product is appropriate to reduce triglycerides and increase HDL-cholesterol levels in patients at high cardiovascular risk who are not adequately controlled with a statin alone.

The legal basis for this application refers to Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/92/2009 on the granting of a waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2. Manufacturers

Manufacturer responsible for batch release

Abbott Healthcare SAS
Lieu-dit Maillard
Route de Belleville
F-01400 Châtillon sur Chalaronne
France

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Alar Irs

- The application was received by the EMA on 21 December 2011.
- The procedure started on 25 January 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 April 2012.
- During the meeting on 24 May 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 25 May 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 December 2012.
- During the meeting on 8 January 2013, the Pharmacovigilance and Risk Assessment Committee (PRAC) adopted RMP Advice and assessment overview.
- During the CHMP meeting on 17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding Issues on 15 February 2013.
- During the meeting on 7 March 2013, the Pharmacovigilance and Risk Assessment Committee (PRAC) adopted RMP Advice and assessment overview.
- During the CHMP meeting on 20 March 2013, outstanding issues were addressed by the

applicant during an oral explanation before the CHMP and the CHMP adopted a second list of outstanding issues via written procedure on 5 April 2013.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 May 2013.
- During the meeting on 16 May 2013, the Pharmacovigilance and Risk Assessment Committee (PRAC) adopted RMP Advice and assessment overview.
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a third list of outstanding issues to be addressed in writing by the applicant and the assessment report was adopted via written procedure on 3 June 2013.
- The applicant submitted the responses to the CHMP third list of outstanding issues on 5 June 2013.
- During the meeting on 12 June 2013, the Pharmacovigilance and Risk Assessment Committee (PRAC) adopted RMP Advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 12 June 2013.
- During the meeting on 27 June 2013, 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 Cholib.

2. Scientific discussion

2.1. Introduction

Hypercholesterolemia, represented by elevated levels of low density lipoprotein cholesterol (LDL-C), is a well-known and studied dyslipidaemia associated with increased risk for CHD. Statin treatment is highly effective for lowering serum levels of LDL-C. Nevertheless, mixed dyslipidaemia associated with low levels of high-density lipoprotein cholesterol (HDL-C) and/or elevated triglycerides, which are risk factors independent of high LDL-C levels, is common.

Cholib is a fixed combination containing two lipid-lowering agents with different mechanisms of action, Fenofibrate is a Peroxisome Proliferator-Activated Receptor (PPAR)α agonist and simvastatin is an inhibitor of 3-Hydroxy-3-MethylGlutaryl-Coenzyme A(HMG-CoA) reductase. The product is formulated as immediate-release film-coated tablets containing 145 mg fenofibrate with either 20 mg or 40 mg of simvastatin. The products are of similar dimensions and are distinguished by their colour and inscription.

Combination of lipid-lowering agents is proposed in relevant scientific guidelines to reach secondary goals beyond LDL-C, such as Non-HDL-cholesterol (Non-HDL-C) and to improve TG and HDL-C. Fibrates have accrued sufficient evidence with regard to reduction of triglycerides and elevation of HDL-C in the several trials, e.g. ACCORD lipid and FIELD trial in diabetics. These

results also formed the basis of the current development programme for Cholib. Fenofibrate product information states that fenofibrate is effective in reducing the VLDL- and LDL-cholesterol in placebo controlled trials in addition to reducing triglycerides by 40-55% and increasing HDL-C by 10-30%. The claimed LDL-C reduction is around 15-30%.

The co-prescription of statins and fibrates to further improve the lipid profile beyond the beneficial effect obtained with statin monotherapy has been studied in numerous clinical studies. The inclusion of the combination lipid lowering therapy in clinical practice was limited by the absence of demonstrated clinical benefit in intervention studies to date and the observation of muscle adverse events, with rare cases of rhabdomyolysis.

The target pharmacodynamic properties of the combination are therefore based on a potentially beneficial addition of the properties of fenofibrate and simvastatin as lipid lowering agents. Based on the complementary effects of fenofibrate and simvastatin and the safety of the co-administration at standard doses, the overall objective of the development program was to evaluate the efficacy and safety of fenofibrate 145 mg and simvastatin 20 and 40 mg as co-administration in patients with mixed dyslipidemia at risk of cardiovascular diseases with no history of muscular disease that are not controlled by simvastatin, pravastatin or atorvastatin in monotherapy. During the procedure the proposed indication was changed to target adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase HDL C levels when LDL C levels are adequately controlled with the corresponding dose of simvastatin monotherapy 20 mg or 40 mg.

Fenofibrate and simvastatin have been registered as monotherapies in the EU *via* national procedures.

2.2. Quality aspects

2.2.1. Introduction

Cholib is a fixed dose combination containing two well-known active substances described in the European Pharmacopeia fenofibrate and simvastatin.

The finished product is presented as film-coated tablets in two strengths respectively containing 145 mg fenofibrate/20 mg simvastatin and 145 mg fenofibrate/40 mg simvastatin as active substances.

Other ingredients are: butylhydroxyanisole, lactose, sodium laurilsulfate, starch pregelatinised (maize), docusate sodium, sucrose, citric acid monohydrate, hypromellose, crospovidone, magnesium stearate, silicified microcrystalline cellulose (comprised of cellulose, microcrystalline and silica, colloidal anhydrous) and ascorbic acid.

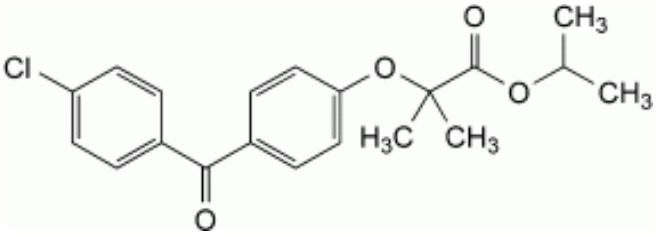
Moreover for the coating: polyvinyl alcohol -partially hydrolysed, titanium dioxide, talc, lecithin (derived from soya bean), xanthan gum and iron oxide red. The lower strength also contains: iron oxide yellow and sunset yellow FCF.

The product is available in Alu/Alu blisters, in two pack sizes of 10 and 30 film-coated tablets.

2.2.2. Active Substance

Fenofibrate

The chemical name (IUPAC) of fenofibrate is propan-2-yl 2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate, its molecular formula C20H21ClO4 and relative molecular mass 360.8 g/mol. It has the following structure:



This active substance is used as the micronized form. Fenofibrate appears as a white to off-white crystalline powder, practically insoluble in water, very soluble in methylene chloride and slightly soluble in ethanol (96 %). As fenofibrate has no ionisable group, its water solubility is not influenced by the pH.

As there is a monograph of fenofibrate in the European Pharmacopoeia, the manufacturers of the active substance have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for this active substance. The CEPs have been provided within the current Marketing Authorisation Application.

Manufacture

Fenofibrate may be manufactured by two manufacturers, both covered by a CEP. The relevant information has been assessed by the EDQM before issuing the CEP.

The active substance is further micronised in different sites to obtain the required particle size. This step is not covered by the CEP. The applicant has confirmed that fenofibrate is routinely micronised irrespective of the particle size of the material. The micronisation is done in an air-jet mill. In order to obtain the required particle size distribution pattern, the operating parameters of dosing speed and air pressure are set and are regularly monitored throughout the micronisation process. The overview of the micronisation procedures, provision for recycling or reprocessing and the process validation have been presented and are acceptable.

Specification

The control tests were carried out to comply with the specifications and test method of the Ph. Eur. monograph, as confirmed by the CEP. Additional specifications have been set for the particle size tested by laser diffraction. This additional method has been adequately validated and described according to ICH Q2.

Batch analysis data (3 production scale batches) from each manufacturing site of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

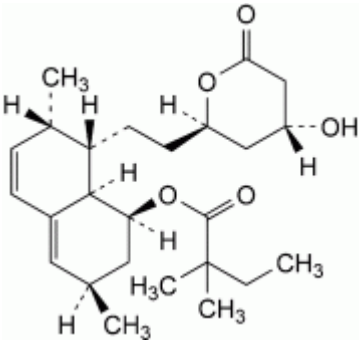
Stability data on three production scale batches of micronised active substance from the first manufacturer and one from the second stored in a container closure system representative of that intended for the market for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

In addition, photostability studies were performed on two lots from the first manufacturer in line with the ICH Q1B guideline. A very slight yellowing of fenofibrate powder was observed after light exposure. Nevertheless, the impurity profile remained unchanged. These results demonstrated the photostability of the fenofibrate.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage for fenofibrate (micronized) in double polyethylene bags in a fibre drum is acceptable.

Simvastatin

The chemical name (IUPAC) of simvastatin is (1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-Hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8ahexahydronaphthalen-1-yl 2,2-dimethylbutanoate, its molecular formula is C25H38O5 and relative molecular mass 418.6 g/mol. It has the following structure:



This active substance is a white or almost white, crystalline powder practically insoluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 %).

As there is a monograph of simvastatin in the European Pharmacopoeia, the manufacturers of the active substance have both been granted CEPs, which were provided within the current Marketing Authorisation Application.

Manufacture

Simvastatin from two manufacturers is used for the finished product. The relevant information has been assessed by the EDQM before issuing the CEPs.

Specification

The control tests were carried out to comply with the specifications and method of the Ph.Eur. monograph, as confirmed also by the two CEPs provided. Additional tests were carried out in line for Butyl hydroxyl anisole (HPLC), Residual solvent (GC) and the particle size as indicated in the CEP.

Batch analysis data (three commercial scale batches from the first manufacturer and two form the second) of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

The CEP of each active substance manufacturer includes a suitably validated re-test period in a defined container closure system.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Cholib is an immediate-release tablet proposed in two dosage strengths: fenofibrate 145 mg / simvastatin 20 mg and fenofibrate 145 mg / simvastatin 40 mg. The tablets are manufactured by mixing a fenofibrate granulate and a simvastatin granulate, blending, compression, and coating. This fixed combination was developed with the intention to address the medical need to control all relevant lipid parameters in mixed dyslipidaemia.

Fenofibrate granulate is obtained from a process for another fenofibrate product marketed by the applicant in many EU member states. The strategy was to utilise the spray granulation intermediate (SGI) of the fenofibrate 145 mg tablets in combination with a granulated source of simvastatin. Manufacture of the SGI involves the conversion of fenofibrate into a nanocrystal colloidal dispersion (NCD). This technology ensures rapid dissolution of the fenofibrate and a rapid onset of action and comparable pharmacokinetic profile as the marketed formulation. The SGI is then incorporated into a tablet which demonstrates no difference in absorption between fed and fasted state. The formulation was further optimised to obtain a stable fenofibrate NCD and subsequently a redispersible granulate which is the major component of the dosage form. The final formulation was also optimised with regard to the crystalline state of sucrose.

Simvastatin granulate was based on an authorised simvastatin product. It is known that simvastatin absorption is not affected by food. It is also known that simvastatin is susceptible to oxidative degradation. In order to produce a stable formulation, the inclusion of an antioxidant in the formulation is required. Pharmaceutically acceptable antioxidants classified as GRAS (Generally Regarded As Safe) were considered as part of the formulation. As the qualitative composition of the authorised simvastatin product includes butylated hydroxyanisole (BHA), citric acid, and ascorbic acid as antioxidants and stabilizers, investigations were performed on how to include these in the simvastatin granulate. Different options of incorporating BHA in the simvastatin granulate were explored. Based on the qualitative composition of the authorised simvastatin product, ascorbic acid was also added as stabiliser while citric acid was considered necessary to complex with metal ions which otherwise act as a

source of free radicals and thus initiate oxidative degradation. After several granulation and PK studies starch was selected as a binder because of a trend in bioequivalence with the authorised simvastatin product. Simvastatin granulate is also manufactured by wet granulation.

Matrix and bilayer tablets prototype formulation were investigated and the results led to the selection of the matrix granulate. A film coating to reduce any potential effect of moisture in the stability of the tablets was chosen.

The first pharmacokinetic study in humans (PK1) was performed with uncoated tablets. However the formulation used during the rest of the clinical studies was the same that the one used for marketing.

The pivotal clinical studies were carried out by co-administration of fenofibrate and simvastatin monotherapy tablets and the applicant has carried out one bioequivalence studies for each strength of the proposed combination product with the products administered in clinical trials (see clinical part).

Comparative dissolution data were provided for the batched tested in the in vivo studies. The dissolution profiles were found similar and any differences have been properly justified. Further dissolution data, in support of the bioequivalence study, have been submitted in accordance with the guidelines, however replacement batches had to be used as the test and reference products used in the bioequivalence study had in the meantime expired.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards apart from film-coat Opadry and Silicified Microcrystalline Cellulose which are controlled by suitable specifications. There was no novel excipients used in he finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two compatibility studies were carried out and demonstrated that fenofibrate was not affected by simvastatin. It was shown that any degradation products formed may be detected and quantified by the analytical methods used to control the finished medicinal product.

The primary packaging is an Alu/Alu blister. The choice of the container has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from human or animal origin have been used in the manufacture of Cholib with the exception of lactose. It was confirmed that it is produced from milk from healthy animals in the same conditions as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. Appropriate BSE/TSE statements were provided for lactose monohydrate and magnesium stearate.

Manufacture of the product

The manufacturing process consists of six main steps: preparation of fenofibrate granule intermediate, preparation of simvastatin granule intermediate, preparation of fenofibrate – simvastatin blend intermediate product, compression of tablet core, film-coating and finished product packaging. The process is considered to be a standard manufacturing process except

for the production of the fenofibrate SGI. The validation data for the manufacturing process of fenofibrate SGI were presented at commercial scale and demonstrated that the process is well controlled within the defined manufacturing parameters.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The critical steps of the manufacturing scheme were identified and suitable in-process controls and holding times have been set. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specification include appropriate test for this kind of dosage form: appearance (visual examination), identification (HPLC and UV), identification and assay of antioxidants (HPLC), degradation products (HPLC), assay (HPLC), content uniformity (Ph. Eur.), moisture content (KF), dissolution (Ph. Eur.), microbial purity (Ph. Eur.).

Batch analysis results were provided for three pilot scale batches for each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches per strength of finished product, stored under long term conditions for 24 months at 25ºC / 60% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. The batches of Cholib were packed in the primary packaging proposed for marketing. Confirmation was provided that the first three commercial scale batches of both strengths will be put in stability tested.

The following parameters were studied using the release specification methods: appearance, content of fenofibrate and its degradation products, content of simvastatin and its degradation products, dissolution of fenofibrate and simvastatin, and microbiological quality (only tested at initial and 24 months).

In addition photostability studies were carried out on two batches of each strength in accordance with ICH guidelines. All batches showed a slight decrease in content of fenofibrate and simvastatin after exposure to light. However, all the batches remained within the specifications. No significant changes were seen in percentage of specified and unspecified impurities during exposure to light.

Based on the available data the shelf life and storage conditions as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead

to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

Cholib is a fixed combination of two lipid-lowering agents with different mechanisms of action: Fenofibrate being a Peroxisome Proliferator-Activated Receptor (PPAR) α-agonist, and simvastatin being an inhibitor of 3-Hydroxy-3-MethylGlutaryl-Coenzyme A (HMG-CoA) reductase.The use of the therapeutic classes of such medicinal products in combination is well known.

2.3.2. Pharmacology

Primary pharmacodynamic studies

There is sufficient evidence of their primary pharmacodynamic effects of the individual components, fenofibrate and simvastatin, and the conduct of specific primary pharmacodynamics studies with the combination is not considered necessary.

Fenofibrate is a prodrug rapidly hydrolysed by esterases to the active metabolite fenofibric acid. It is commonly held that the pharmacologic effects of fenofibrate are therefore attributable to fenofibric acid. Fenofibrate demonstrates a wide range of effects on the synthetic and catabolic pathways involved in lipids, carbohydrates and amino acid metabolism, and has been effectively used for years for the treatment of dyslipidemia. Fenofibrate results in significant decreases in plasma triglycerides as well as decreases in total cholesterol, LDL-C, VLDL-C, apoB, and apoC-III, an inhibitor of lipoprotein lipase. In conjunction with these decreases, there are concomitant increases in HDL-C and its major constituents apoA-I and apoA-II, as well as apoC-II, a stimulator of lipoprotein lipase.

Simvastatin is a pro-drug hydrolysed in the liver to the active metabolite β-hydroxyacid simvastatin and four other active metabolites. Clinical trials have demonstrated that simvastatin prevents cardiovascular events and reduces mortality in primary and secondary prevention of ischemic heart disease. Simvastatin reduces both normal and elevated LDL cholesterol concentrations. LDL is formed from VLDL and is catabolised predominantly by the high affinity LDL receptor. The LDL-lowering mechanisms of simvastatin may involve both reduction of VLDL cholesterol concentrations and induction of the LDL receptor leading to reduced production and increased catabolism of LDL cholesterol. Apo B also falls substantially during treatment with simvastatin. In addition, simvastatin slightly increases HDL cholesterol and reduces plasma triglycerides.

Secondary pharmacodynamic studies

Simvastatin and fenofibrate are drugs extensively used for many years and, therefore, were evaluated in a number of experimental models.

In cell-free assays, fenofibrate modulated the membrane rigidity and, in mice given fenofibrate, the $A\beta_{42}$ form of the amyloid peptide in their brains increased, possibly because fenofibrate caused structural changes in γ-secretase, the enzyme responsible of $A\beta_{42}$ production. Similarly, simvastatin was shown to have negative effects on nerve myelinisation *in vitro.*

No secondary pharmacodynamic studies were conducted with the fixed combination of Cholib. This is acceptable since the potential off-target effect on vital organs is sufficiently addressed in the SmPC of these approved medicinal products.

Safety pharmacology programme

No non-clinical safety pharmacology studies were conducted with the fixed combination since the concomitant clinical use of fenofibrate and simvastatin was not reported to be associated with unexpected side-effects. The effects of fenofibrate and simvastatin on skeletal muscles are reported in the toxicology section.

In vitro, fenofibrate had anti-proliferative effects on cardiomyocytes and inhibited the hypertrophy of rat cardiomyocytes. Fenofibrate markedly inhibited the endothelin-1 (ET-1)-induced increase in c-Jun gene expression and phosphorylation of c-Jun. These results suggest that fenofibrate interferes with the formation of activating protein-1 (AP-1) induced by ET-1 in cardiomyocytes. In a rat model of heart failure, dosing with fenofibrate for 11 weeks inhibited the development of left ventricle (LV) hypertrophy, attenuated the LV relaxation abnormality and systolic dysfunction and improved the survival rate. This was accompanied by the inhibition of the pro-inflammatory pathways of NF-κB and AP-1. In another model of rat infarct-induced heart failure, fenofibrate given for 12 weeks resulted in an up-regulation of the fatty acid metabolic pathway but did not improve LV hypertrophy or dysfunction. Fenofibrate was also shown to reduce the LV hypertrophy in another rat model, and its effect was potentiated by the PPARgamma agonist rosiglitazone.

Simvastatin induced apoptosis of rat primary cardiomyocytes but, in synergy with losartan, prevented angiotensin II-induced apoptosis of cardiomyocytes. Simvastatin induced

mitochondrial impairment and alteration of Ca^{2+} homeostasis in permeabilised but not in intact rat ventricular cardiomyocytes.

In a pig model of "no-reflow" (an incomplete myocardial reperfusion after acute myocardial infarction, despite complete restoration of epicardial vessel blood flow), pre-treatment with simvastatin significantly increased coronary blood flow, decreased the area of no-reflow and reduced the necrotic area. Fenofibrate was ineffective in this model but was shown beneficial in two other pig models. In pacing-induced heart failure in pigs, fenofibrate attenuated the reduction in left ventricular ejection, reduced cardiac hypertrophy and clinical signs of heart failure. In a coronary angioplasty pig model, fenofibrate inhibited constrictive remodelling and neointima formation through inhibition of inflammation and adventitial neovascularisation.

Simvastatin decreased coenzyme Q (CoQ) modulated resistance to oxidative stress. Mice given simvastatin had reduced levels of oxidised and reduced CoQ_9 and CoQ_{10} in serum, liver, and heart. In addition, cultured cardiac myocytes treated with simvastatin exhibited less resistance to oxidative stress, decreased time to the cessation of spontaneous beating in response to H_2O_2 addition, and decreased responsiveness to electrical field stimulation. These effects were alleviated by the co-administration of CoQ_{10} with simvastatin. In a rat model of hypertension induced by chronic L-NAME administration, simvastatin decreased concentrations of both CoQ homologues in the heart and slightly decreased CoQ_9 concentration in the skeletal muscle. No effects were observed on hepatic CoQ level. In the same model, simvastatin was shown to attenuate the inhibition of NO-synthase activity in kidney and brain, partly prevented the development of hypertension and reduced the concentration of cardiac CoQ. Nevertheless, myocardial hypertrophy, fibrosis and remodelling of the aorta were not prevented.

Potential effects of fenofibrate and simvastatin on vital systems other than cardiovascular, i.e. CNS, respiratory, renal and digestive systems are adequately reflected in the proposed SmPC.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted with the fixed combination of Cholib. Based on the date available for simvastatin and fenofibrate, and the review of literature, it can be concluded that possible pharmacodynamic interactions of the fixed combination with other drugs are those of each drug considered separately.

Of importance are the clinically-documented potentiating effects of fenofibrate and simvastatin on oral, vitamin K-dependent anticoagulants. Therefore, the CHMP requested that the SmPC of the fixed combination of Cholib reflects these properties. In patients taking the fixed combination of fenofibrate and simvastatin, an oral anticoagulant therapy should be started with a reduced dose and then gradually adjusted according to INR monitoring, as advised in the SmPC.

Interaction between the PPARα and the statin signalling pathways which would provide opportunities for pharmacodynamic interactions has been reported. This interaction between their signalling pathways could also lead to synergism between fenofibrate and simvastatin for the unintended effects of the combination.

2.3.3. Pharmacokinetics

As the pharmacokinetics of the two well-known mono-components fenofibrate and simvastatin were extensively investigated and are considered well described, no absorption, distribution, metabolism and excretion studies have been conducted with the fixed combination Cholib.

Fenofibrate

Absorption: After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. The maximum plasma concentrations of fenofibric acid occur within 2 to 4 hours after oral administration.

Distribution: The tissue radioactivity concentration in [14C]-Fenofibrate on 0.5, 4, 8, 24, 72, and 168 hours after single oral administration to Sprague-Dawley rats was measured. The highest concentration 30 minutes after administration was found in the liver, the kidney and the stomach corresponding to 2 to 3 times the plasma concentration. Between 4 to 24 hr, the highest concentrations are found in the liver (2.5 to 4 times the plasma concentration) and the kidney (1.2 to 2 times the plasma concentration).

The protein binding rate of plasma concentration was about 99% for both male and female rats. The transfer of radioactivity to milk was investigated following the oral administration of $^{[14C]}$fenofibrate to lactating rats on the 10th day after delivery. The radioactivity in the milk reached a maximum at 12 hours after the dosing, and decreased with a half-life of 10 hours from 12 to 48 hours. The AUC of radioactivity in the milk was 7 times higher than that in the plasma.

Metabolism: In vitro studies using human liver microsomes indicated that fenofibrate and fenofibric acid are not inhibitors of the CYP isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at concentrations of 30-50 µM. They were also found to be moderate inhibitors of CYP2B6 and CYP2C8 in human hepatic microsomes. Fenofibrate and fenofibric acid are not substrates of the membrane transporter P-glycoprotein (P-gp), but showed moderate P-gp inhibition in vitro. Fenofibrate and fenofibric acid showed a concentration-dependent inhibition of the human organic anion transporting-polypeptide 1B1 in vitro, at IC50 without clinical relevance when considering fenofibric acid concentrations actually achieved in clinical practice. Fenofibrate showed no significant inhibition of multidrug resistance protein 2 in vitro.

Excretion: Fenofibrate and its glucuronide conjugate are excreted mainly in the urine. Practically all the drug is eliminated within 6 days. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

Simvastatin

Absorption: In human, simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin.

Distribution: Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6-hydroxy, 6-hydroxymethyl, and 6-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours post-dose.

Metabolism: Simvastatin is catalysed primarily by CYP3A4/5 with a minor contribution from CYP2C8. Glucuronidation of the dihydroxy side chain is a metabolic pathway for simvastatin. The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites.

Excretion: Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors of HMG-CoA reductase.

Pharmacokinetic drug interactions

No non-clinical pharmacokinetic drug interactions studies were conducted with the proposed fixed combination of Cholib. Based on the available data for simvastatin and fenofibrate, and the review of scientific literature the CHMP concluded that potentials for drug-drug interactions with the fixed combination of simvastatin and fenofibrate are those of each drug considered separately. Fenofibrate is not a substrate for CYP 3A4 and no hepatic microsomal metabolism is involved. Fenofibric acid and its glucuronide conjugate are excreted mainly in urine.

Of particular importance is the fact that simvastatin is a substrate of CYP 3A4. Therefore, potent inhibitors of CYP 3A4 increase the concentration of HMG-CoA reductase inhibitory activity and the subsequent risks of skeletal muscle toxicity. Concomitant treatment with potent CYP 3A4 inhibitors is contraindicated. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors. Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via CYP 3A4.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies and no repeat-dose toxicity studies were conducted with the fixed-combination of fenofibrate and simvastatin. This is acceptable and in line with the CHMP guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005), which states that safety studies in animals are not required for fixed combinations with sufficiently documented human experience of their individual and combined use.

Repeat dose toxicity

No repeat-dose toxicity studies were conducted with the fixed-combination of fenofibrate and simvastatin. Nevertheless, an update of results is provided on recently conducted repeat-dose toxicity studies with fenofibric acid, the active metabolite of fenofibrate, in the Sprague-Dawley rat and the beagle dog in order to support the clinical development of fenofibric acid choline salt. The dose levels were selected to compare the data with those from earlier toxicity studies submitted with the previous applications. These studies are summarised in table below.

Summary of the Recent Repeat-Dose Toxicity Studies Conducted with Fenofibrate or Fenofibric Acid

Species	Strain	Group	Mode of Administration	Test Material	Doses mg/kg/day (a)	Duration (wks)
Rat	Sprague-Dawley	15M + 15F	Oral (gavage)	Fenofibric acid choline salt	0, 30, 100, 300	2
	Sprague-Dawley	15M + 15F	Oral (gavage)	Fenofibric acid calcium salt	0, 30, 100, 300	2
	Sprague-Dawley	10M + 10F	Oral (dietary admixture)	Fenofibric acid	0, 10, 30, 75, 150	5
	Sprague-Dawley	10M + 10F	Oral (dietary admixture)	Fenofibrate	0, 100, 300	5
	Sprague-Dawley	15M + 15F	Oral (gavage)	Fenofibric acid choline salt	0, 10, 30, 100	13
Dog	Beagle	2M + 2F	Oral (capsules)	Fenofibric acid	0, 30, 100, 300	2
	Beagle	2M + 2F	Oral (capsules)	Fenofibric acid,	100	2
				Fenofibric acid choline salt	0, 75, 150, 225	2
	Beagle	6M + 6F	Oral (capsules)	Fenofibric acid choline salt	0, 25, 50, 100	13

(a) Dose levels of fenofibric acid free acid or calcium or choline salt are given in mg free acid/kg

The two pivotal 13-week studies in rat and dog with fenofibric acid choline salt were designed to achieve plasma exposures to fenofibric acid matching those observed in the earlier repeat-dose toxicity studies with fenofibrate. The results show that fenofibric acid exposures in both 13-week studies are equal to or higher than those described after chronic dosing with fenofibrate to rats (78-week chronic study) and dogs (52-week chronic study).

Plasma Exposure to Fenofibric Acid in Rat and Dog Repeat-Dose Toxicity Studies Conducted with Fenofibrate or Fenofibric Acid Choline Salt, and Comparison with Human data

Species and Duration	Dosing with Fenofibrate		
	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg.h/mL)
Rat	20[a]	33.2	384
(78-week ; diet)	80[a]	161.2	2647
	320[a]	394.0	7388
Dog	25	12.7 – 16.8	88 – 136

(52-week ; capsules)	100	40.6 – 41.3	360 – 427
	400	77.6 – 97.4	1167 – 1470
Human (single dose)	(200 mg/70 kg ≈ 2.9)	8.6	147

Species and Duration	Dosing with Fenofibric Acid		
	Dose for PK (mg acid/kg)	C_{max} (µg/mL)	AUC (µg.h/mL)
Rat	10	40.9 –45.9	527 – 530
(13-week ; gavage)	30	183 – 188	2586 – 3209
	100	609 – 679	12021 - 12194
Dog	25	53.1 – 64.1	222 – 272
(13-week ;capsules)	50	115 – 144	833 – 1098
	100	225 – 245	1887 – 2565
Human (repeat dose)	(135 mg acid/70 kg ≈1.9)	12.1	183

(a)PK data available only after single dosing from a different study

In the rat studies, no test-article related mortalities were observed in the two-week gavage and the five-week diet studies. In the 13-week gavage study one high dose male was found dead on day 83, due to unknown reasons. Only at the high dose levels body weight gain and food consumption were reduced relative to control animals, which indicates good tolerability of fenofibric acid and fenofibrate. In the two-week studies at 100 and 300 mg acid/kg/day the animals showed a slight decrease in the red blood cell parameters and abnormal red blood cell morphology. These results suggested an accelerated removal of red blood cells with membrane abnormalities and a corresponding physiologically appropriate increase in erythropoiesis. Changes in the liver were noted in rats from all studies, with increases in liver enzyme values more pronounced in males than in females. Heart lesions of focal loss and degeneration of myofibers and infiltration of mononuclear inflammatory cells were found in male rats dosed with fenofibric acid at 30 and 100 mg acid/kg/day. Higher absolute and/or relative heart weights in rats were also observed. Although previous studies of fenofibrate in rats did not reveal cardiac findings, the direct head-to-head comparison of fenofibrate and fenofibric acid in the five-week diet studies showed these lesions in both studies. Male rats seem to be more sensitive towards this toxicity than females and the lesions occurred at approximately 22-fold the human exposure.

Degeneration in muscles from the caudal thigh characterised by scattered myofibres infiltrated with phagocytic cells was observed at ≥ 100 mg acid/kg/day in the two-week gavage studies, at ≥ 75 mg acid/kg/day in the five-week dietary study with fenofibric acid and 300 mg/kg/day in the five-week dietary study with fenofibrate, and at 100 mg acid/kg/day in the 13-week gavage study. The lesions occurred primarily in the soleus muscle at about 60-80 fold the human exposure. It was also demonstrated that skeletal muscle degeneration occurred in muscles known to have the greatest density of myofibres that stained positive to slow myosin, suggesting that slow oxidative myofibres were selectively affected.

In the 13-week study with dogs, one male dog in the 100 mg acid/kg/day dosage group (about 13-fold the clinical exposure) was euthanized on day 39 due to severe weight loss (~30%). Treatment-related clinical observations were limited to sporadic emesis, and reduced mean body weights in dogs given 50 and 100 mg acid/kg/day relative to control dogs. A dose-dependent decrease in the red blood cell mass, an increased activated partial thromboplastin time and slight increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were seen in the 50 and 100 mg acid/kg/day groups; none of these changes were evident at the

end of the 6-week drug-free period. Minimal single-cell necrosis of liver was accompanied by minimal to mild mixed inflammatory cell infiltrates at 50 and 100 mg acid/kg/day. The findings fully reversed during the six-week drug-free period. Ulcerations, erosions and mucosal atrophy were seen in the high dose groups of the 2-week studies (225 or 300 mg acid/kg/day). In the 13-week study moderately decreased mean ovary weights that correlated microscopically with immaturity were seen in all females from 25 mg acid/kg/day onwards. Testicular tubular vacuolation was seen in the 2-week and the 13-week studies where young dogs were administered fenofibric acid free acid or choline salt. By 13 weeks of dosing, the vacuolation was associated with hypo-spermatogenesis from the low dose onwards (25 mg acid/kg/day, <1.5-fold the human exposure). None of these changes was noted in animals allowed the supplementary six-week drug-free period.

Genotoxicity

No genotoxicity studies were conducted with the fixed combination of Cholib because the combination of the two active substances into a single tablet has not been associated with new impurities or degradation products resulting from chemical or physico-chemical interactions between fenofibrate and simvastatin.

Based on literature data, fenofibrate was not genotoxic in a battery of *in vitro* and *in vivo* assays, including the Ames reverse mutation test, gene mutations in *S. cerevisiae* or mouse lymphoma assay, chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells, induction of unscheduled DNA synthesis in primary rat hepatocytes, as well as metaphase analysis of bone marrow from fenofibrate gavaged SD rats or increase in DNA synthesis in the testis of CD-1 mice given fenofibrate. In case of simvastatin, no evidence of mutagenicity was observed in a microbial mutagenicity Ames test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Carcinogenicity

No carcinogenicity studies were conducted with the fixed combination of Cholib. As there is no evidence to suggest a greater carcinogenicity risk when fibrates and statins are co-administered this approach is acceptable to the CHMP.

Reproduction Toxicity

No new reproductive and developmental toxicity studies have been initiated with the fixed-combination. The reproductive and developmental toxicity (fertility and early embryonic, embryofetal and pre- and post natal development potentials) of the two substances are well known and no additional risks are expected during co-administration. As described in section on Repeat dose toxicity studies, in young dogs (9-12 months at necropsy), there were effects on testes and ovaries at all the doses tested, but the clinical significance of these findings is not known. Nevertheless, adequate information on these non-clinical data has been included in the SmPC of Cholib. Furthermore, simvastatin is currently contraindicated during pregnancy and lactation, based mainly on theoretical effects on the concepts due to the impairment of the

biosynthesis of cholesterol. Consequently, Cholib is also contraindicated during pregnancy and lactation.

Toxicokinetic data

No specific toxicokinetic studies were conducted with Cholib. Supplementary information on pharmacokinetic parameters of fenofibric acid after repeated oral administration were obtained from the toxicokinetic measurements in recent toxicity studies conducted in rats and dogs as discussed in section on Repeat dose toxicity studies.

Local Tolerance

No non-clinical local tolerance studies were performed with the fixed combination, due to the route of application and the existing clinical experience. No specific lesions of the stomach were found in the recent repeat toxicity studies conducted with fenofibric acid or fenofibrate in rats. In dogs, ulcerations, erosions and mucosal atrophy were seen in the high dose groups of the 2-week studies (225 or 300 mg acid/kg/day) and are reflected in the SmPC of Cholib.

Other toxicity studies

Fenofibrate and simvastatin are well-established use substances when used separately. No concerns regarding their potential immunotoxicity, antigenicity, or drug dependence have been identified during their clinical use in monotherapy or as a free combination. Therefore, no other specific toxicity studies were considered with the fixed combination. Since fenofibrate is contraindicated in patients with known photo-allergic or photo-toxic reactions to fenofibrate or ketoprofen, the SmPC of Cholib is also contraindicated in this patient group.

2.3.5. Ecotoxicity / environmental risk assessment

Since Cholib is intended for a substitution of two already approved products, this will not lead to an increased exposure to the environment. The justification of the lack of ERA is thus acceptable to the CHMP. Fenofibrate and simvastatin are already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore the fixed dose combination of fenofibrate and simvastatin is not expected to pose any additional risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical profiles of fenofibrate and simvastatin are well documented and literature references have been provided to address the pharmacodynamic, pharmacokinetic and toxicology of these substances. No new pharmacodynamic, safety pharmacology or pharmacokinetic studies were conducted, which is acceptable and in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). Repeat dose toxicity studies were recently conducted with fenofibric acid in dogs and rats and these provide updated information on its toxicological profile, which is adequately reflected in the SmPC of Cholib. Furthermore, as concluded by the CHMP, the

fixed dose combination of fenofibrate and simvastatin is not expected to pose any additional risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical data provided in support of the marketing authorisation of Cholib sufficient and there are no measures to be addressed in the post-authorisation phase.

2.4. Clinical aspects

2.4.1. Introduction

Both, fenofibrate and simvastatin, are known lipid modifying agents and have been used for a number of years in clinical practise in the EU and worldwide. The clinical programme of a fixed combination of fenofibrate 145 mg and simvastatin 20/40 mg is based on:

- Four phase 3 clinical studies evaluating the efficacy and safety of co-administration of fenofibrate 145 mg and simvastatin 20 and 40 mg in patients with mixed dyslipidemia remaining hypertriglyceridemic and hypercholesterolemic after statin monotherapy.
- Two pivotal bioequivalence studies to bridge clinical results obtained with the co-administration of the two separate products - and two fixed combination tablets fenofibrate 145 mg/simvastatin 20 mg and fenofibrate 145 mg/simvastatin 40 mg.
- Supportive documentation coming from published clinical studies and evaluation of safety databases of these two well established-use lipid-modifying agents.

GCP

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

- Tabular overview of clinical studies

List of bioavailability studies

Studies	**Comparators**	**No of FDCs compared**	**Subjects**
KLF0242780-01 05 01 KH	145 mg/ 40 mg (FF/SV)	2 FDCs	Male HVs (n=17)
KLF0242780-01 05 02 KH		One FDC	Male HVs (n=23)
KLF0242780-01 05 03 KH		Three FDCs	Male HVs (n=20)
KLF0242780-01 07 01 KH	145 mg/ 20 mg (FF/SV)	Two FDCs	Male HVs (n=23)

List of Bioequivalence studies

Studies	Comparators	Subjects Recruited/ Completed	Design	Analytes	Parameters
S285.01.001	FDC; F-145/S-20 Vs F-145 + S-20	150/ 145 Male HVs	Replicate, 4 period, 2 seq	Fenofibric acid, Simvastatin & Simvastatin Acid	Cmax, AUCt, AUCi
S285.01.002	FDC; F-145/S-40 Vs F145 +S40	148/ 144 Male HVs			

List of Interaction studies

Studies	Comparators	Subjects Recruited/ Completed	Design	Analytes	Parameters
KLF178T 03 02 KH	S 40 Vs F145+ S40	12 Male HVs	Open, 2 way, randomised, X-over,	Fenofibric acid, Simvastatin & Simva Acid	Cmax, AUCt, AUCi

Clinical Efficacy/ Safety studies

Study ID	No. of study centres	Study Posology	Subjects by arm entered/ completed.	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
LF0242780-01 05 01	N=99 EU wide	F145/S 20 then 40 vs S 40	FS 526/ 458 S 524/481	• 6Wk run in • 24 Wk DB • 28 Wk Ext	705M / 345 F 56.1 yrs	CHD/ CHD risk Euiv; NCEPIII	• **Sup** for TG and HDL-C over S40 • **NI** for LDL-C (4%) margin at 12 wks
LF0242780-01 05 02	N=63 EU/ Aust/ NZ	F145/S40 Vs S40	FS 225/215 S 224/205	• 6wk run-in • 24wk DB	355 M /94F 55.9 yrs.	CHD/ CHD risk Euiv; NCEPIII	• Superiority over S40 at 12 wks
LF0242780-01 05 03	N=54; EU & Ukraine	F145 / S20 then 40 Vs Atorv 10 & 20	FS 276/246 A 272/246	• 6Wk run in • 24 Wk DB • 28 Wk Ext	374M / 174F 55.1 Yrs	CHD/ CHD risk Euiv; NCEPIII	• **Sup** for TG and HDL-C over A10; • **NI** vs A10 for LDL-C at 12 weeks
LF0242780-01 05 04	N=58; EU, Russia and South Africa	F145/ S20 & 40 Vs Prava 40	FS 210/186 Vs Pr 210/95	• 6Wk run in • 24 Wk DB • 28 Wk Ext	347M / 73F 54.5 Yrs	CHD/ CHD risk Euiv; NCEPIII	• **Sup** for TG and HDL-C over P40 • **NI** for LDL-C (4%) margin at 12 wks

Sup= Superiority; NI = Non-inferiority; CHD= Coronary heart disease; TG- triglycerides; HDL-C= high density lipoprotein cholesterol

2.4.2. Pharmacokinetics

Absorption, Distribution, Elimination

Both components of the fixed combination have been in clinical use for several years and their pharmacokinetic (PK) properties were determined at the time of their development. No specific bioavailability studies have been considered for the development of the fixed combination.

Two pivotal studies (S285.1.001 and S285.1.002) were performed to test the bioequivalence between fixed combination fenofibrate/simvastatin tablets and the co-administration of individual tablets. Four bioavailability studies (KLF0242780-01 05 01 KH, KLF0242780-01 05 02 KH, KLF0242780-01 05 03 KH, and KLF0242780-01 07 01 KH) were conducted to aid in the selection of the final dosage forms to be tested in the pivotal bioequivalence studies. Phase 3 clinical trials were performed with the co-administration of individual tablets instead of fixed-combination tablets containing fenofibrate and simvastatin. Both, fenofibrate and simvastatin, are Biopharmaceutics Classification System (BSC)-class II, defined as high permeability and low solubility. A summary of the Absorption, distribution, elimination data of each mono-component is provided below.

Fenofibrate

Maximum plasma concentrations (C_{max}) occur within 2 to 4 hours after oral administration. Plasma concentrations are stable during continuous treatment. Contrary to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of the nanoparticules formulation is independent from food intake. Fenofibric acid is highly protein bound (>99%) and kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibrate is not a substrate for CYP 3A4 and the drug is excreted mainly in the urine mainly in the form of fenofibric acid or its glucuronide conjugate. Fenofibric acid is not eliminated by haemodialysis and the plasma elimination half-life of fenofibric acid is approximately 20 hours.

Simvastatin

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is slow. Simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption. Simvastatin is highly protein bound (>95%) and does not accumulate on repeated dosing. Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. Following an intravenous (IV) injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours.

Due to the extent of the clinical knowledge and experience with fenofibrate and simvastatin either in monotherapy or in co-administration at the time of development, no additional risk was expected from the use of the fixed combination and it was therefore considered unnecessary to perform pharmacokinetic studies examining the influence of intrinsic factors on exposure with the fixed combination.

Bioequivalence studies

In order to bridge the clinical studies that were conducted with the co-administration of fenofibrate (145mg) and simvastatin (20mg or 40mg) to the proposed fixed dose combination, the applicant conducted two bioequivalence studies: one study with the 20 mg simvastatin (S285.1.001) and the other with the 40 mg simvastatin (S285.01.002). The dose of fenofibrate was 145mg. Both studies used the open label, randomised, replicate, 4 period, 2 sequence design with 10 day washout period between studies. The sample size was adequate for both studies (n=150 and n=148 respectively) with 143 and 140 subjects completing all 4 sequences. The main results of these studies are presented in the table below.

Results of bioequivalence studies

Study		**S285.1.001**		**S285.1.002**	
Parameter		***Point Est***	***90% CI***	***Point Est***	***90% CI***
Fenofibric acid					
	AUC_t	0.998	0.987-1.010	1.020	1.008 – 1.032
	C_{max}	0.970	0.954- 0.987	1.032	1.012 – 1.051
Simvastatin					
	AUC_t	1.002	0.959 – 1.048	0.892	0.858 – 0.927
	C_{max}	0.692	0.659 – 0.727	0.939	0.897 – 0.983
Simvastatin acid					
	AUC_t	1.165	1.115 – 1.216	1.082	1.045– 1.120
	C_{max}	1.081	1.029 – 1.134	1.121	1.077– 1.166

The CHMP raised questions about the appropriateness of calculations using below limit of quantitation (BLQ) and exclusion of data. The applicant provided re-evaluated PK parameters and statistical analysis not replacing BLQ with the half value of lower limit of quantitation (LLOQ). Bioequivalence was demonstrated for simvastatin and for simvastatin acid also after recalculation. No recalculation was needed for fenofibric acid since no samples between two measurable samples were BLQ. With regard to number of subjects excluded from the PK analysis, it was shown that the number of subjects excluded due to >50% of samples missing was the same for C_{max} and AUC_t. The number of subjects excluded varied for AUC_{inf} since no AUC_{inf} was calculated when R2 was <0.8 or area extrapolated was more than 20%.

In the S285.1.002 study the 145/40 mg fixed combination tablet fulfilled the acceptance criteria for bioequivalence; all parameters had 90%CI between 0.80-1.25 as per the standards outlined in the CHMP bioequivalence guideline (CHMP/EWP/QWP/1401/98/Rev.1).

Based on the statistical analysis and results, the applicant stated that treatment A (SLV285 fenofibrate 145 mg, simvastatin 20 mg combination tablet) was found to be bioequivalent to treatment B (fenofibrate 145 mg tablet + simvastatin 20 mg tablet) also in Study 285.1.001. However, C_{max} of simvastatin (geometric least squares mean ratio of 0.692 and 90%CI of 0.659 to 0.727) was outside the acceptance range of [0.75-1.33]. The applicant claimed that the acceptance range for C_{max} was widened because the within-subject variability for C_{max} of the reference compound in the study was >30%. Since the 90% CI also fails to meet these widened acceptance criteria, whether or not it is agreed that use of widened criteria is appropriate becomes a moot point. In this study, as well as in the bioavailability 07-01 KH study, the fixed

dose formulation was not shown to be bioequivalent with the coadministered combination as per the standards outlined in the CHMP bioequivalence guideline (CHMP/EWP/QWP/1401/98/Rev.1).

Overall, the provided data aim to establish bioequivalence such that similar efficacy and safety between the free combination of the two agents and the fixed dose combination is expected. The usual standards are met for the high strength of the combination, but not for the low strength. The CHMP raised this issue as a major objection. The applicant stated that only C_{max} for simvastatin (the 'parent' compound) was outside of the bioequivalence acceptance limits and only in one study (S285-01-001) but AUC for the lower strength and all parameters for the higher strength in study S285-01-002 were within the acceptance criteria of 80-125%. There is also an aspect of 'multiple testing' here such that one or multiple tests may fail by chance alone, even where products are truly bioequivalent. It is also argued that C_{max} of the parent compound has minimal clinical importance if total exposure is shown to be equivalent, in particular in light of the AUC and C_{max} results on the main active metabolite, which meet the standard criteria. In the context of this particular application, and in light of the clinical data provided, this single point estimate and confidence interval does not give sufficient grounds for objection and the lower dose strength can be accepted.

Food effect

The applicant presented arguments that the current formulation of the fixed combination of fenofibrate and simvastatin does not exhibit a food effect. A study report for study KLF K178P 0206 KH 0302 examining the potential food effect was presented. The PK results for fenofibric acid with arithmetic means (SD) and associated coefficient of variation (CV) are summarised below.

Comparison high fat fed (Reg A) versus fasting (Reg C) [study K LF K178P 0206 KH 0302]

HFF versus Fasting				
Parameter n = 44 (PKS)	**Geometric Mean HFF (Regimen A)**	**Geometric Mean Fasting (Regimen C)**	**Point Estimate**	**90% CI**
AUC	124.8	118.5	**1.052**	1.018 – 1.088
AUCt	123.0	116.5	**1.054**	1.020 – 1.090
Cmax	7.82	7.77	**1.007**	0.963 – 1.054
LFF versus Fasting				
AUC	119.8	118.5	**1.012**	0.978 – 1.046
AUCt	118.1	116.5	**1.013**	0.981 – 1.047
Cmax	7.84	7.77	**1.009**	0.964 – 1.055

PKS: pharmacokinetic sample, HFF: high fat fed, LFF: low fat fed

The results of the study alleviate the concerns about the food effect on the micronised formulation of fenofibrate and thus, it is concluded that food has negligible influence on the 145mg fenofibrate tablet. It is assumed that there is no food effect on the fixed combination product. Adequate wording has been included in the SmPC of Cholib.

Dose proportionality and time dependencies

Dose proportionality, time dependency and other PK characteristics are considered adequately documented for the mono-components and no other specific studies were considered necessary.

Special populations

Within the development programme, certain special subpopulations were studied and these included subjects with renal impairment, subjects older than 65 years, and women. Although the studies were not specifically designed to investigate these subgroups, the distribution of patients allowed for such subgroup analysis. In the group with renal insufficiency (n=204), comparison of subsets based on their eGFR (30-59ml/min/1.73m^2 or $\geq$ 60 mL/min/1.73m^2) showed that the incremental reduction of TG and increase of HDL were both higher for the FDC when compared to simvastatin alone. There were no subjects with eGFR <30ms (an exclusion criterion) and therefore no conclusion can be drawn. There was a consistent gender effect on the treatment, although these data were generated within the main pivotal studies and not in specific gender-based studies. It appears that the fixed dose combination has less effect in males, a high risk group despite the changes in TG and HDL-C, however, the clinical implications are not considered to be significant.

Pharmacokinetic interaction studies

Results of two interaction studies were originally provided by the applicant: a primary interaction study conducted within the development programme and a published study on interaction between simvastatin and fenofibrate. Both studies were conducted in approximately 12 subjects and were of a conventional with a two period, two treatment crossover comparison of the combination (simvastatin+fenofibrate) to the simvastatin alone arm. In Study KLF178T 03 02 KH, 12 healthy male subjects aged 20 to 39 years (mean: 29.2 $\pm$ 6.9years) received two treatments: treatment A was a 160 mg fenofibrate tablet once daily for 10 days and a 40 mg simvastatin tablet as a single dose simultaneously with the last dose of fenofibrate; treatment B was a 40 mg simvastatin tablet as a single dose. To assess the effect of fenofibrate on simvastatin PK, simvastatin and simvastatin acid, log-transformed AUC, AUC_{0-t}, and C_{max} were compared between day 11 of treatment A and day 1 of treatment B using an analysis of variance (ANOVA) followed by the calculation of the 90% confidence interval (CI) for the ratios of the geometric least-squares means. Decrease in simvastatin acid exposure (-42%) was observed for AUC upon co-administration with fenofibrate. No effect was observed on C_{max}, as confirmed by the 90% CI [0.794 to 1.260] which was close to the required limits, with a point estimate of 1.000.

The clinical study published by Bergman et al (J Clin Pharmacol, 2004; 44:1054-62) investigated the interaction between 80mg simvastatin and 160mg of micronised fenofibrate in a phase I study in 2004 in 12 subjects. In all 25 subjects were enrolled and PK data from 12 who completed the study were analysed and used for comparison. Of note, the first 12 subjects enrolled were discontinued due to errors in pharmacokinetic sample processing. A new cohort of 13 subjects was enrolled, which included 1 replacement subject, and 12 completed. Simvastatin acid AUC_{0-24h} was 36% lower when simvastatin was administered with fenofibrate compared with simvastatin alone.

The applicant claims that the interaction noted has no clinical relevance. The arguments presented include that as simvastatin acid is only one component that contributes approximately

25% of all active HMG-CoA reductase inhibitors in plasma, the modest decrease in simvastatin acid AUC_{0-24h} was consistent with the small decrease in active HMG-CoA reductase inhibitor AUC_{0-24h}. However, this finding is from a single study and lacks detail on how the active and total HMG-CoA inhibitory activity was evaluated. Indeed, both interaction studies are small and affected by technical issues. The KLF178T-03-02-KH study only analysed the simvastatin hydroxy acid and no other metabolite or inhibitor activity while the Bergman study estimated the overall inhibitor activity but failed to assay other specific HMG-Co-A inhibitors. If the interaction is seen with FDC/co-administration and also when the two active substances are separated by a time profile, this could provide reassurance that the clinical relevance of this interaction was small since there exist considerable amounts of clinical data with the free association where efficacy was demonstrated in spite of this interaction. This is addressed in M13-953 below.

Clinical study M13—953

The additionally conducted study M13—953 in healthy volunteers which evaluates the interaction further and also if any interactions occur during staggered administration. The design of the study and protocol are acceptable apart from the value to use lipid profiles as PD effect after 7 days of treatment in each period.

Eighty-five healthy volunteers (54 males and 31 females) were randomized, 79 completed the three treatment periods and 81 were included in the pharmacokinetic analysis. The pharmacokinetic data on Day 1 after single dose of simvastatin alone or simvastatin plus fenofibrate did not show significant interaction in terms of exposure. The design and results at steady state are summarised in tables below for the parent drug simvastatin and the metabolite simvastatin acid. The steady state of fenofibric acid was reached since its trough concentrations did not change between the last three days of administration.

Dosing schedule of clinical study M13-953

Treatment		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
A	Morning	-	-	-	-	-	-	-
	Evening	S	S	S	S	S	S	S
B	Morning	-	-	-	-	-	-	-
	Evening	F/S	F/S	F/S	F/S	F/S	F/S	F/S
C	Morning	F	F	F	F	F	F	F
	Evening	S	S	S	S	S	S	S

S: Simvastatin 40 mg F: Fenofibrate 145 mg

The overview of results from clinical study M13—953

Simvastatin	**Mean (SD) AUC_{0-24}** (ng*h/mL)	30.0 (12.0)	29.1 (10.9)	29.0 (11.6)
	Mean (SD) Cmax (ng/mL)	9.9 (7.0)	10.0 (5.5)	10.3 (7.2)
	Median Tmax (h)	1.5	1.5	1.5
Simvastatin acid	**Mean (SD) AUC_{0-24}** (ng*h/mL)	23.7 (17.2)	18.0 (11.0)	16.3 (10.8)
	Mean (SD) Cmax (ng/mL)	2.4 (1.6)	2.7 (1.2)	2.2 (1.3)
	Median Tmax (h)	5.0	3.0	4.0
		Geometric mean ratio (90% CI) B/C	**Geometric mean ratio (90% CI) B/A**	**Geometric mean ratio (90% CI) C/A**
Simvastatin	**AUC_{0-24}**	101 (96-106)	98 (94-103)	97 (93-102)
	Cmax	100 (90-111)	102 (92-114)	102 (92-114)
Simvastatin acid	**AUC_{0-24}**	111 (102-121)	79 (73-86)	71 (65-78)
	Cmax	128 (119-138)	120 (111-130)	94 (87-101)

While the applicant has taken comparison of B/C rather than A vs B or A vs C (as per table above) as the primary comparison, in order to evaluate the actual effect of the interaction, the primary comparisons should have been with simvastatin monotherapy (A). The claim that interaction is marginally (but not statistically) different in favour of FDC (21% *vs* 29% reduction in simvastatin acid AUC) could only be sustained if the mechanism of interaction was explained. It is claimed that there is no induction of enzyme pathways or transporters but this is followed by a statement that the level of interaction is not expected to increase. This is a strong assumption given the absence of an understanding of the mechanisms involved. Indeed, the applicant, having reviewed the literature, was unable to find specific indicators of this interaction or an explanation for the finding in the two studies in the mechanistic context. The co-administration of fenofibrate and simvastatin has led to a reduction of simvastatin acid exposure without changing simvastatin exposure. This suggests that fenofibrate interferes with biotransformation of simvastatin and/or simvastatin acid. However, this is not supported by *in vitro* data; in particular the biotransformation of simvastatin acid by human hepatocytes is not modified by co-incubation with fenofibrate. As discussed above, extensive literature search as well as an additional *in vitro* plasma protein displacement study did not reveal any putative cause of the observed interaction. Thus, based on these data, a firm conclusion on what the direct cause of the AUC reduction in simvastatin acid when simvastatin and fenofibrate are co-administered cannot be reached and remains to be explored.

The key conclusions from this study are that it confirms the pharmacokinetic interaction between the two components (reduction in exposure to simvastatin acid in the presence of fenofibrate) but that the reduction appears to be of comparable magnitude regardless of whether the components are administered together (B) or separated by 12 hours (C). Of course, this finding is based on this single study only and with some uncertainty around the estimated effect sizes.

Pharmacokinetics using human biomaterials

Due to the extent of the clinical knowledge and experience either in monotherapy or in co-administration at the time of development it was considered unnecessary to perform studies examining pharmacokinetics using human biomaterials with the fixed combination. Therefore no

such studies related to hepatic metabolism, drug interaction or plasma protein binding are presented.

2.4.3. Pharmacodynamics

Mechanism of action

The lipid modifying effects of fenofibrate (a fibric acid derivative) in humans are mediated *via* activation of PPARα. Through activation of PPARα, fenofibrate increases the lipolysis and elimination of atherogenic TG-rich particles from plasma by activating lipoprotein lipase and reducing production of apo CIII. Activation of PPARα also induces an increase in the synthesis of apo AI and apo AII.

Simvastatin, an inactive lactone is hydrolysed in the liver to the corresponding active beta-hydroxyacid form, which is a potent inhibitor of HMG-CoA reductase. Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations.

Primary and Secondary pharmacology

The individual pharmacodynamic profiles for fenofibrate and simvastatin are well known, and information on the pharmacodynamic effects of fenofibrate and simvastatin are described in the literature. The target pharmacodynamic properties of the combination are based on a beneficial addition of the properties of fenofibrate and simvastatin as lipid lowering agents. Considering the extent of clinical knowledge and experience to date, the properties of the individual compounds are not expected to be different from those observed when both components are given together as a free combination. As a consequence, no pharmacodynamic studies have been conducted with the fixed-combinations of fenofibrate/simvastatin 145/20 mg and fenofibrate/simvastatin 145/40 mg.

As both fenofibrate and simvastatin have previously demonstrated reduction of LDL-C, it is expected that the combination will produce additive effects on LDL-C in the clinical trials. This is further discussed in the section on Clinical efficacy.

2.4.4. Discussion on clinical pharmacology

Simvastatin and fenofibrate are established lipid-lowering monotherapies and their pharmacokinetics and pharmacodynamics properties are well known. Due to the extent of the clinical knowledge and experience either in monotherapy or in co-administration at the time of development it was considered unnecessary to perform new studies examining primary pharmacokinetics or pharmacodynamics using human biomaterials. Therefore no such studies related to hepatic metabolism, drug interaction or plasma protein binding are presented. Of the four bioavailability studies, the applicant has selected two fixed dose combinations to be taken forward for further clinical development. Bioequivalence was achieved for the 40 mg strength, but full bioequivalence was not achieved for the 20 mg strength for the C_{max} of the parent compound. For the lower strength, only one of multiple tests fails to meet the bioequivalence criteria. It is also argued that C_{max} of the parent compound has minimal clinical importance if total exposure is shown to be equivalent, in particular in light of the AUC and C_{max} results on the

main active metabolite, which meet the standard criteria. In the context of this particular application, and in light of the clinical data provided, this single point estimate and confidence interval does not give sufficient grounds for objection and the lower dose strength can be accepted.

The potential food effect seen with other medicinal products containing fenofibrate was avoided for Cholib due to the use of micronised fenofibrate and nanocrystal technology for the formulation, so that the fenofibrate absorption is enhanced. Thus, the maximum plasma concentration and overall exposure of this formulation is independent from food intake. A food-effect study involving administration of this formulation of fenofibrate 145mg tablets to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_{max}) to fenofibric acid is not affected by food. Therefore Cholib may be taken without regard to meals. This is adequately reflected in the SmPC.

Pharmacokinetic interaction between simvastatin and fenofibrate were investigated which show that there is an appreciable level of interaction resulting in reduction of the AUC of simvastatin acid when simvastatin and fenofibrate are administered together either after a single dose of simvastatin or in steady state. This was investigated in two studies and the clinical significance of the interaction has to be considered. In the first, smaller study, the magnitude of reduction of AUC was estimated to be 42% (study K LF178T 03 02 KH) after single dose and 36% in steady state (Bergman et al study, 2004). The M13-953 study further characterised this interaction. The key conclusions from this study are that it confirms the pharmacokinetic interaction between the two components (reduction in exposure to simvastatin acid in the presence of fenofibrate) but that the reduction appears to be of comparable magnitude regardless of whether the components are administered together or separated by 12 hours. Of course, this finding is based on this single study only and with some uncertainty around the estimated effect sizes. This study also evaluated the lipid lowering effect of the combination (FDC and concomitant administration) and provided evidence that neither was there a difference between these administrations, nor between either of these modes of administration and simvastatin alone. As the study duration was limited to 7 days, no confirmatory inference can be drawn regarding the long-term effects, and this must be sought from the longer-term clinical studies that are available from the clinical programme. As discussed below, interpretation of the clinical studies are complex, in particular since they were designed to support a different therapeutic indication (representing a higher hurdle that the indication finally proposed and agreed). Nevertheless, these clinical data are supportive, confirming an effect of the simvastatin component on LDL-C levels based on the weight of evidence from the pivotal studies from the applicant and the ACCORD study publication. Based on the evidence that the interaction is not greater for the FDC than the free association, even when administered at different times, these clinical data showing the maintenance of the beneficial effect on LDL-C for simvastatin used in combination compared with simvastatin alone offer adequate reassurance. Any risk is likely to be mitigated by using the combination only when LDL-C levels are controlled by optimal statin dose, reflecting the restricted indication as agreed by the CHMP.

All other drug interactions reported for the monotherapies are adequately captured in the SmPC of Cholib.

2.4.5. Conclusions on clinical pharmacology

The individual pharmacodynamic and pharmacokinetic profiles of simvastatin and fenofibrate are well known. The mechanisms of actions are expected to be complementary for the proposed therapeutic use of Cholib. All concerns of the CHMP, in particular those relating to pharmacokinetic interactions and bridging between the FDC formulation and free association, were addressed by the applicant and the CHMP agreed that no further post-authorisation measures are necessary.

2.5. Clinical efficacy

2.5.1. Dose response study

Based on the fact that both active substances, simvastatin and fenofibrate, have been in clinical use for a number of years and there are extensive data available to account for dose response for each of the mono-therapies, no detailed investigation on dose-finding were conducted. However, within the clinical development programme, i.e., the efficacy studies, two dose formulations of the fixed dose combination with different doses of simvastatin were included and provide additional data relating to the dose response. Fenofibrate has been used at a single dose of 145 mg in all clinical studies and this is indeed the dose included in the fixed combination of Cholib, with a forced titration of statin doses to demonstrate the changes in lipid parameters. The selected doses are considered validated by widespread clinical practice and by the efficacy results observed in the pivotal studies.

2.5.2. Main studies

The efficacy of Cholib has been mainly tested in four main clinical studies: Study C LF0242780-01 05 01 (referred thereafter as study 0501), Study C LF0242780-01 05 02 (study 0502), Study C LF0242780-01 05 03 (study 0503) and Study C LF0242780-01 05 04 (study 0504). These were supported by results from five published double-blind studies with fenofibrate or fenofibric acid and simvastatin (which also include the long-term studies i.e., FIELD and ACCORD lipid.) All four main studies were of a similar design of comparing the FDC with either a forced titration of statin doses (in two studies simvastatin in 0501, atorvastatin 0503) or a constant dose in 0502 and 0504 (40mg simvastatin and 40mg of pravastatin respectively) from the start.

Title of Study

Study C LF0242780-01 05 01: A multicenter, double-blind, randomized, active comparator, forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 20 mg simvastatin alone.

Study C LF0242780-01 05 02: A multicenter, double-blind, randomized study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease

not adequately controlled by 40 mg simvastatin alone.

Study C LF0242780-01 05 03: A multicenter, double-blind, randomized, forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with atorvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 10 mg atorvastatin alone.

Study C LF0242780-01 05 04: A multicenter, double-blind, randomized forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with 40 mg pravastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 40 mg pravastatin alone.

Study	Treatment Duration Study Design	Population	No of Treated Subjects	Fenofibrate Dosage (mg)	Statin Dosage (mg)	Conditions to Use Coadministration and/or Inclusion Criteria Baseline Median TG and Mean LDL-C and HDL-C (after statin-run in pivotal studies; without treatment in other studies) Units are mg/dL - NA not available)			
							TG	LDL-C	HDL-C
C LF0242780-01 05 01	6 months rando, DB, PG (2 arms) 6 months OP	Mixed dyslipidemia	526 524	F145 -	S20/40 S40	TG > 150 LDL-C and/or non-HDL-C > NCEP target after 6 weeks S20	219 223	131 132	47 48
C LF0242780-01 05 02	6 months rando, DB, PG (2 arms)	Mixed dyslipidemia	225 224	F145 -	S40 S40	TG > 150 LDL-C and/or non-HDL-C > NCEP target after 6 weeks S40	232 228	127 128	47 47
C LF0242780-01 05 03	6 months rando, DB, PG (2 arms) 6 months OP	Mixed dyslipidemia	276 272	F145 -	S20/40 A10/20	TG > 150 LDL-C and/or non-HDL-C > NCEP target after 6 weeks A10	211 214	129 130	47 47
C LF0242780-01 05 04	6 months rando, DB, PG (2 arms) 6 months OP	Mixed dyslipidemia	210 210	F145 -	S20/40 P40	TG > 150 LDL-C and/or non-HDL-C > NCEP target after 6 weeks P40	208 215	138 143	46 46

Methods

The design of the pivotal studies was largely similar. All subjects were first included in a 6-week open-label run-in period with statin monotherapy. Subjects not adequately controlled by statin were randomized in a 24-week double-blind period (DB) using the run-in statin as the control treatment. In all studies except the 0502, the subjects who completed the double-blind period entered a 28-week open-label extension period.

Study Participants

The patient population consisted in subjects with mixed dyslipidemia, at risk for coronary heart disease or cardiovascular disease, who had no history of muscle disease and whose dyslipidemia was not controlled by simvastatin, atorvastatin or pravastatin monotherapy.

The inclusion/exclusion criteria were the same in all studies: male or female subjects, between 18 and 75 years, presenting with CHD or CHD risk equivalent (excluding diabetes) per NCEP ATPIII in whom 10-year risk for CHD was more than 20% or with no CHD but with multiple risk factors (≥ 2). The Framingham score at randomization had to be ≥ 10%. At randomization,

subjects had TG ≥ 1.71 mmol/L and <4.00 mmol/L. In subjects with CHD or CHD risk equivalent in whom 10-year risk for CHD was >20%, LDL-C was ≥ 2.58 mmol/L but <4.91 mmol/L or Non-HDL-C ≥ 3.36 mmol/L but <5.69 mmol/L. In subjects with multiple risk factors equivalent in whom 10-year risk for CHD was 10 to 20%, LDL-C was ≥ 3.36 mmol/L but <5.69 mmol/L or Non-HDL-C ≥ 4.13 mmol/L but < 6.46 mmol/L.

Pregnant and lactating women were excluded, as subjects with known type 1 or type 2 diabetes. Amongst other factors excluding subjects were known active or chronic hepatobiliary or liver diseases, known cholelithiasis, current chronic pancreatitis, alcoholism, medical history of myositis, myopathy or rhabdomyolysis, known abnormal thyroid hormone levels, uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins, renal failure or renal dysfunction, congestive heart failure class III or IV, uncontrolled cardiac arrhythmias, myocardial infarction, coronary bypass surgery or angioplasty within three months of inclusion in the study, unstable or severe peripheral artery disease within three months of inclusion in the study, any other severe pathology such as cancer or mental illness or degenerative disease that would limit study evaluation or participation.

Treatments

Study	Dosing and administration
C LF0242780-01 05 01	Run-in period: simvastatin 20 mg Double-blind treatment period: - fenofibrate 145 mg + simvastatin 20 mg for 12 weeks (feno145+simva20) and forced titration to fenofibrate 145 mg + simvastatin 40 mg (feno145+simva40) for 12 weeks or - Placebo fenofibrate + simvastatin 40 mg for 24 weeks (simva40).
C LF0242780-01 05 02	Run-in period: simvastatin 40 mg Double-blind treatment period: - fenofibrate 145 mg + simvastatin 40 mg for 24 weeks (feno145+simva40) or - Placebo fenofibrate + simvastatin 40 mg for 24 weeks (simva40).
C LF0242780-01 05 03	Run-in period: atorvastatin 10 mg Double-blind treatment period: - fenofibrate 145 mg + simvastatin 20 mg for 12 weeks (feno145+simva20) and forced titration to fenofibrate 145 mg + simvastatin 40 mg for 12 weeks (feno145+simva40) or - Placebo fenofibrate + atorvastatin 10 mg for 12 weeks (atorva10) and forced-titration to Placebo fenofibrate + atorvastatin 20 mg for 12 weeks (atorva20).
C LF0242780-01 05 04	Run-in period: pravastatin 40 mg Double-blind treatment period: - fenofibrate 145 mg + simvastatin 20 mg for 12 weeks (feno145+simva20) and forced titration to fenofibrate 145 mg + simvastatin 40 mg for 12 weeks (feno145+simva40) or - Placebo fenofibrate + pravastatin 40 mg for 24 weeks (prava40).

In all studies except 0502, the subjects who completed the double-blind period entered an open extension period, while they were first treated with fenofibrate 145mg+simvastatin 20mg for six weeks. Then, subjects who did not achieve the National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III)1 LDL-C and/or TG goals had their treatment uptitrated to fenofibrate 145mg+simvastatin 40mg until the end of the study while the other subjects continued fenofibrate 145 mg+simvastatin 20mg treatment.

Objectives

In studies 0501 and 0503, the primary objective was to evaluate, in subjects not adequately controlled by simvastatin 20 mg and atorvastatin 10 mg respectively, the efficacy of the co-administration of fenofibrate 145 mg and simvastatin 20 mg compared to the statin monotherapy to reduce TG and increase HDL-C without losing efficacy in reducing LDL-C, after 12 weeks of treatment. In studies 0502 and 0504, the primary objective was to evaluate, in subjects not adequately controlled by simvastatin 40 mg and pravastatin 40 mg respectively, the efficacy of the co-administration of fenofibrate 145 mg and simvastatin compared to statin monotherapy to reduce LDL-C and TG and to increase HDL-C after 12 weeks of treatment.

Outcomes/endpoints

The *primary endpoint* was the percent change from baseline to 12 weeks of treatment in TG, HDL-C and LDL-C.

The *secondary endpoints* were treatment effects compared the treatment groups on:

- the percent change from baseline to 24 weeks of treatment in TG, HDL-C and LDL-C;
- the percent change from baseline to 12 weeks and 24 weeks of treatment in Non-HDL-C, TC, LDL size (only for studies 0501 and 0502), ApoAI and ApoB and ApoB/ApoAI ratio;
- the changes from baseline to 12 weeks, and 24 weeks in high sensitive C-Reactive Protein (hs-CRP) and fibrinogen;
- the percentage of subjects reaching the NCEP-ATP III targets after 12 weeks and 24 weeks;
- the percent change from 24 weeks to 30 and 52 weeks of treatment in TG, LDL-C, HDL-C, TC and Non-HDL-C; the percentage of subjects reaching the NCEP-ATP III targets after 30 weeks and 52 weeks and the changes from 24 weeks to 52 weeks in hs-CRP and fibrinogen (except for the study 0502).

Sample size

Calculation of the sample size was based on the co-primary endpoints: percentage change in TG, HDL-C and LDL-C from baseline to 12 weeks of treatment and, according to the individual trial, aimed to show the non-inferiority of the co-administration (145 mg fenofibrate + 20 mg simvastatin) *versus* statin alone on % change in LDL-C. The non-inferiority margin was fixed at 4%, assuming a true mean difference between the 2 groups of 0 and a common standard deviation of 18%, as well as the detection of a mean difference in % change from baseline to 12 weeks treatment of 15% in TG, assuming a common standard deviation of 30% and of 7% in HDL-C, assuming a common standard deviation of 18% in order to show the superiority of the co-administration *versus* statin alone on % change in TG and HDL-C.

Randomisation

The randomisation was stratified by gender and by cardiovascular risk level. As the number of centres was large with regard to the total sample size, the randomisation was not stratified by centre, but a centralised randomisation was used in order to ensure an optimal control of the group balance. Treatments were assigned at the randomisation visit to patients compliant with the inclusion/exclusion/randomisation criteria using four block-balanced randomisation lists.

Blinding (masking)

During the blinded treatment period, statin tablets were over-encapsulated identically in all studies, except the 0502 study for which simvastatin 40 mg tablets were used in both arms, in order to prevent the investigators, the subjects, or the sponsor to identify the treatment. The results of the lipid tests were not provided to the investigators, the trial physicians, the clinical study managers or the monitors, thus, these remained blinded.

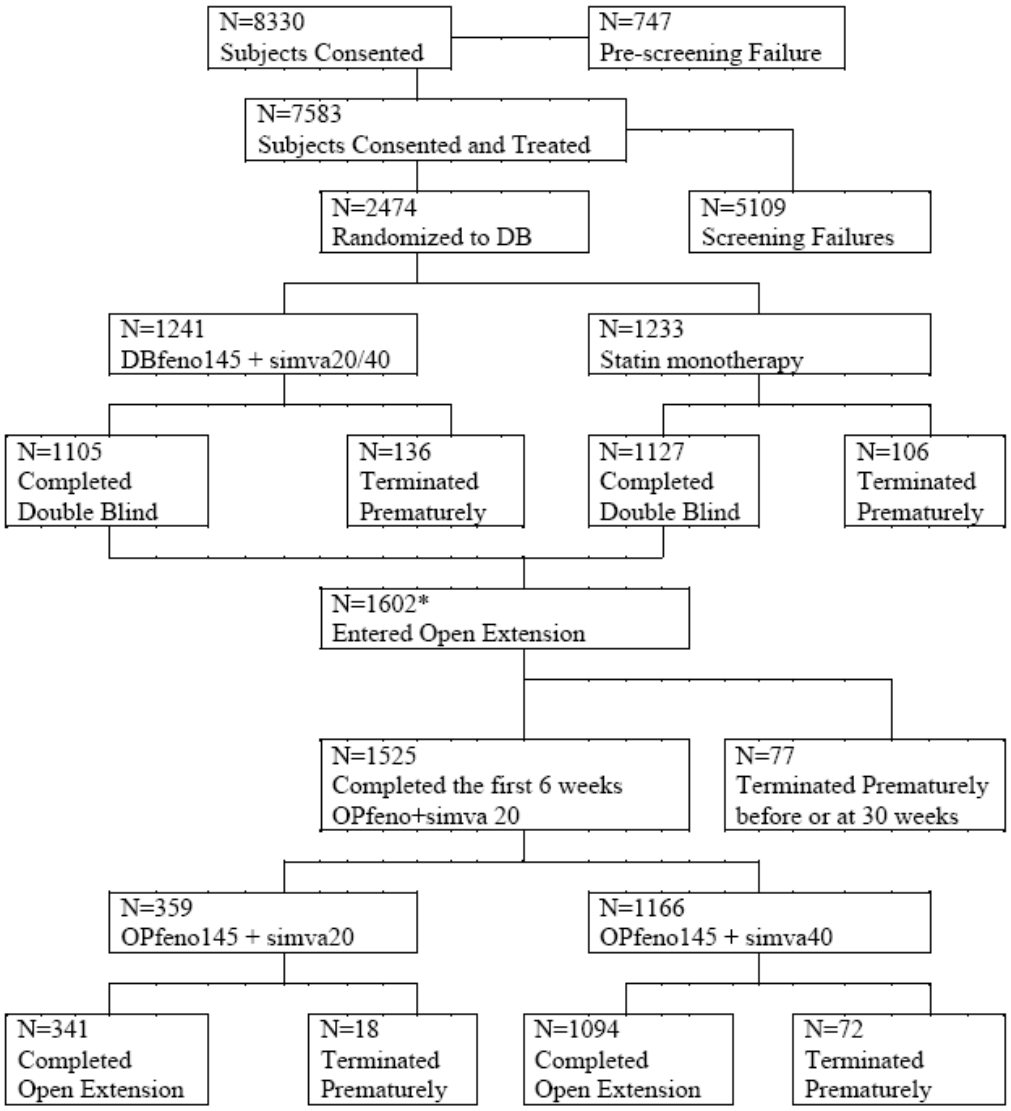
Statistical methods

All trials used ANCOVA approach to analyse the primary analysis data, adjusting for baseline, gender and cardiovascular risk category. Last Observation Carried Forwards was used to impute missing data for the primary endpoint. In order to control the Type I error, all three primary endpoints (LDL-C, HDL-C and TG) were expected to be significant. For HDL-C and TG this was superiority, and for LDL-C this was non-inferiority in 2 studies and superiority in 2. The CHMP agreed that the methods used to analyse the data were acceptable. The method used to handle the missing data were also acceptable and the control of the type I error is appropriate.

Results

Participant flow

The overall patient flow in the complete clinical programme is depicted on the figure below.



Recruitment

All clinical trials were multicentric. Study 0501 was conducted in centres mainly in the EU; study 0502 was conducted in the EU/ Australia/New Zealand; study 0503 was conducted in the EU and Ukraine; study 0504 was conducted in the EU, Israel, Russia and South Africa.

Conduct of the study

No major issues in study conduct were reported by the applicant based on the quality control and assurance activities. The numbers of protocol deviations are acceptable and do not cause any concerns.

Baseline data

Summary of demographic data in the main studies are provided in the table below.

Demographics and Cardiovascular Risk Factors per Study – Subjects treated in the 24-week Double-Blind Period

	0501 N=1050 Mean (SD) or n (%)	0502 N=449 Mean (SD) or n (%)	0503 N=548 Mean (SD) or n (%)	0504 N=420 Mean (SD) or n (%)	Overall N=2467 Mean (SD) or n (%)
Age (yrs)	56.1 (8.3)	55.9 (9.0)	55.1(8.1)	54.5 (9.5)	55.5 (8.6)
Age category					
< 65 years	858 (81.7%)	355 (79.1%)	471 (85.9%)	347 (82.6%)	2031 (82.3%)
≥ 65 yeas	192 (18.3%)	94 (20.9%)	77 (14.1%)	73 (17.4%)	436 (17.7%)
Gender					
Male	705 (67.1%)	307 (68.4%)	374 (68.2%)	286 (68.1%)	1672 (67.8%)
Female	345 (32.9%)	142 (31.6%)	174 (31.8%)	134 (31.9%)	795 (32.2%)
BMI (kg/m²) at Visit 2	29.99 (4.08)	30.75 (4.48)	29.65 (4.10)	30.19 (4.34)	30.08 (4.22)
Patients with CHD	727 (69.2%)	233 (51.9%)	294 (53.6%)	216 (51.4%)	1470 (59.6%)
Smoker	442 (42.1%)	221 (49.2%)	323 (58.9%)	223 (53.1%)	1209 (49.0%)
Hypertensive	915 (87.1%)	409 (91.1%)	510 (93.1%)	358 (85.2%)	2192 (88.9%)
Cardiovascular risk					
High-risk subjects	900 (85.7%)	347 (77.3%)	469 (85.6%)	339 (80.7%)	2055 (83.3%)
Moderately high-risk subjects	150 (14.3%)	102 (22.7%)	79 (14.4%)	81 (19.3%)	412 (16.7%)

The CHMP noted that the study population is as expected based on the inclusion/exclusion criteria. Majority of the subjects are male and of relatively high cardiovascular risk. There were no major imbalances in the study arms at baseline. The exclusion of diabetic patients and patients with recent CV event/intervention reduces the external validity of the results.

Numbers analysed

Overall, 1241 subjects were randomised to and 1237 subjects were treated with the fenofibrate and simvastatin co-administration. Thus, 1233 patients were randomised to and 1230 treated with the statin mono-therapy; please see table overview below.

Populations Evaluated in the Phase 3 Studies

	Co-administration	Statin monotherapy	Overall
Treated in statin run-in period	-	7583	7583
Randomized in double-blind period	1241	1233	2474
Treated in double-blind period	1237	1230	2467
- Analyzed for safety 0-12 weeks	1237	1230	2467
- Analyzed for safety 0-24 weeks*	1204	1194	2398
- Analyzed for efficacy 0-12 weeks (0501, 0503, 0504)	962	976	1938
- Analyzed for efficacy 0-24 weeks	1070	1088	2058
Treated with co-administration in open extension period**	786	816	1602

* 33 subjects randomised to co-administration and 36 randomised to statin monotherapy who received the alternative treatment from 12 to 24 weeks were excluded, **Numbers are given according to randomization: 816 subjects initially randomized to statin monotherapy received co-administration in the extension period.

Outcomes and estimation

The assessment of efficacy was based on the individual and the integrated analyses of the four double-blind randomized studies. The main outcomes in the clinical development programme were changes in lipid parameters in 12 and 24 week observations; lower dose for 12 weeks and higher dose of statins where relevant in the FDC arm for 12 weeks. While 2 of the 4 studies followed the forced titration pattern, it is of note that no long term data in terms of clinical

outcomes were presented. The effect on long term outcomes are assumed based on published evidence accrued over the years for modification of LDL-C, increasing HDL-C and TGs. Of note, the role of TGs as independent risk factor after satisfactory reduction of LDL-C and control of HDL-C are yet unproven even in the mixed dyslipidemia patients. Thus, the clinical discussion below centres around maintenance of long-term lipid modifying effect related to reduction of TGs and LDL-C and increase in HDL-C.

The key primary and secondary parameters for individual and integrated analysis are summarised in the table below.

Parameters for individual and integrated analysis.

Individual and Integrated Analyses of the Phase 3 Program

Study	Subjects Randomized	Primary analyses after 12 weeks of treatment				Key secondary analyses after 24 weeks of treatment			
		Comparison	Criteria*			Comparison	Criteria*		
			TG	LDL-C	HDL-C		TG	LDL-C	HDL-C
0501	1050	F145/S20 vs. S40	Sup	Non-inf	Sup	F145/S40 vs. S40	Sup	Sup	Sup
0502	450	F145/S40 vs. S40	Sup	Sup	Sup	F145/S40 vs. S40	Sup	Sup	Sup
0503	551	F145/S20 vs. A10	Sup	Non-inf	Sup	F145/S40 vs. A20	Sup	Non-inf	Sup
0504	423	F145/S20 vs. P40	Sup	Sup	Sup	F145/S40 vs. P40	Sup	Sup	Sup
Int. Analysis		Analyses of 4 studies after 24 weeks				Analyses of 0501, 0503 &0504 after 12 weeks			
			TG	LDL-C	HDL-C		TG	LDL-C	HDL-C
		F145/S40 vs. statin	Sup	Non-inf	Sup	F145/S20 vs. statin	Sup	Non-inf	Sup

* Sup: Superiority. Non-inf: Non-inferiority,
F: fenofibrate, S: simvastatin, A: atorvastatin, P: pravastatin, Int.: Integrated

The secondary efficacy parameters included: the percent change from baseline to 24 weeks of treatment in TG, HDL-C and LDL-C; the percent change from baseline to 12 & 24 weeks of treatment in Non-HDL-C, TC, LDL size (for studies 0501 and 0502), ApoAI and ApoB and ApoB/ApoAI ratio; the changes from baseline to 12 & 24 weeks in hs-CRP and fibrinogen; the percentage of subjects reaching the NCEP-ATP III targets after 12 weeks and 24weeks; the percent change from 24 weeks to 30 and 52 weeks of treatment in TG, LDL-C, HDL-C, TC and Non-HDL-C; the percentage of subjects reaching the NCEP-ATP III targets after 30weeks and 52 weeks and the changes from 24 weeks to 52 weeks in hs-CRP and fibrinogen (except for the study 0502).

The results of the individual and integrated analyses are presented in the following table.

Results of individual and integrated analysis of all 4 studies

TG, LDL-C and HDL-C at Baseline, 24 Weeks, Percent Change at 24 Weeks from Baseline in Individual Studies and Integrated Analysis

		TG (mmol/L)*		LDL-C (mmol/L)**		HDL-C (mmol/L)**	
		Feno 145 + Simva 20/40	Statins	Feno 145 + Simva 20/40	Statins	Feno 145 + Simva 20/40	Statins
0501	N	422	437	422	438	422	437
	Baseline	2.46	2.54	3.38	3.40	1.24	1.23
	24 weeks	1.58	2.26	3.00	3.03	1.32	1.22
	% change	-39.0	-9.8	-9.7	-9.8	7.4	0.1
	Treatment comparison	-30.7 (-34.4, -26.7)		-0.1 (-3.2, 3.0)		7.2 (5.0, 9.5)	
	P value	<0.001		0.951		<0.001	
0502	N	213	203	213	203	213	203
	Baseline	2.61	2.54	3.27	3.30	1.22	1.22
	24 weeks	1.76	2.56	3.08	3.34	1.28	1.22
	% change	-30.9	-4.1	-4.0	3.1	5.1	0.6
	Treatment comparison	-27.6 (-32.9, -21.8)		-7.2 (-12.2, -2.2)		4.6 (1.9, 7.4)	
	P value	<0.001		0.005		0.001	
0503	N	249	249	249	249	249	249
	Baseline	2.39	2.42	3.34	3.36	1.22	1.22
	24 weeks	1.66	2.26	3.09	3.09	1.29	1.20
	% change	-30.6	-8.2	-6.0	-6.9	7.5	0.0
	Treatment comparison	-23.7 (-29.1, -18.0)		0.7 (-3.7, 5.1)		7.3 (4.3, 10.3)	
	P value	<0.001		§		<0.001	
0504	N	186	198	186	198	186	198
	Baseline	2.34	2.43	3.58	3.68	1.19	1.19
	24 weeks	1.47	2.30	3.03	3.60	1.27	1.19
	% change	-35.5	-6.2	-14.9	-0.2	7.3	1.5
	Treatment comparison	-33.6 (-38.6, -28.2)		-15.5 (-20.2, -10.9)		5.9 (2.4, 9.5)	
	P value	<0.001		<0.001		0.001	
Total	N	1070	1087	1070	1088	1070	1087
	Baseline	2.46	2.49	3.38	3.42	1.23	1.22
	24 weeks	1.61	2.32	3.04	3.20	1.30	1.21
	% change	-35.8	-7.4	-8.6	-5.0	6.9	0.4
Overall fixed	Treatment comparison	-29.1 (-31.5, -26.7)		-4.1 (-6.1, -2.1)		**6.4 (5.0, 7.8)**	
	P value	<0.001		§§		**<0.001**	
Overall random	Treatment comparison	**-29.0 (-32.8, -25.0)**		**-5.4 (-12.7, 1.8)**		6.4 (5.0, 7.8)	
	P value	**<0.001**		§§		<0.001	
Test for heterogeneity		Q=7.50	p=0.058	Q=35.60	p<0.001	Q=2.55	p=0.467

* Median values and median percent changes from baseline; ** Mean values and mean percent changes from baseline;

Treatment comparison consists of the difference between the Least Squares (LS) means for coadministration and statin monotherapy with 95% CI, when presented in bold corresponds to the preferred model.

§ Non-inferiority not demonstrated (upper bound of the CI ≥ non-inferiority margin fixed at 4.0%);

§§ Non-inferiority demonstrated (upper bound of the CI < non-inferiority margin fixed at 4.0%);

Study 0501: After 12 weeks of treatment, combination of fenofibrate 145mg +simvastatin 20mg was superior to simvastatin 40mg in reducing TG and, despite the interaction between treatment and gender, in increasing HDL-C in both female and male subjects, as well as in the whole population. The sensitivity analysis on percent change in LDL-C showed a statistically significant interaction between gender and treatment that did not allow concluding on the effect on LDL-C in the overall population. After 24 weeks of treatment, the superiority of fenofibrate 145mg + simvastatin 20/40mg over simvastatin 40mg in reducing TG, increasing HDL-C and reducing LDL-C in female subjects was maintained. The interaction between treatment and gender persisted and the superiority of fenofibrate 145mg +simvastatin 20/40mg compared to simvastatin 40mg in reducing LDL-C in male subjects was not demonstrated.

Study 0502: After 12 weeks of treatment, fenofibrate 145mg + simvastatin 40mg was superior to simvastatin 40mg in reducing TG and increasing HDL-C levels. A significant interaction

between treatment and gender did not allow concluding on the effect on LDL C in the overall population. The superiority of fenofibrate 145mg + simvastatin 40mg over simvastatin 40mg was shown in female subjects only. After 24 weeks of treatment, the superiority of fenofibrate 145mg + simvastatin 40mg over simvastatin 40mg in reducing TG and increasing HDL-C was maintained. Similar treatment and gender interaction was seen as in study 501.

Study 0503: The fixed dose combination of simvastatin and fenofibrate was compared with 10 and 20 mg atorvastatin. After 12 weeks of treatment, fenofibrate 145mg + simvastatin 20mg was superior to atorvastatin 10mg in reducing TG and increasing HDL-C levels. The sensitivity analysis on percent change in LDL-C showed a statistically significant interaction between gender and treatment that did not allow concluding on the effect on LDL-C in the overall population but changes from baseline observed in both treatment groups were similar. Non-inferiority of fenofibrate 145mg +simvastatin 20mg compared to atorvastatin 10mg on LDL-C reduction was shown in females only. After 24 weeks of treatment, the superiority of fenofibrate 145mg +simvastatin 20/40mg over atorvastatin 10/20mg in reducing TG and in increasing HDL-C was maintained despite an interaction between treatment and gender for HDL-C. The non- inferiority of fenofibrate 145mg + simvastatin 20/40mg compared to atorvastatine 10/20mg in reducing LDL-C was not demonstrated.

Study 0504: Safety of the co-administration of fenofibrate 145 mg and simvastatin 20 or 40 mg with pravastatin 40 mg and its efficacy to reduce TG and LDL-C and increase HDL-C after 12 and 24 weeks of treatment was compared. After 12 weeks of treatment, feno145+simva20 was superior to prava40 in reducing TG and in increasing HDL-C. Despite a significant interaction between treatment and gender the superiority of the co-administration in reducing LDL-C was shown in both male and female subjects and in the whole population. After 24 weeks of treatment, the superiority of co-administration over prava40 in reducing TG and in increasing HDL-C was maintained, while LDL-C reduction was improved. Of the 4 studies, this was the only study to convincingly show the superiority of fenofibrate+ simvastatin over 40 mg pravastatin, but this is unsurprising.

The summary of efficacy for combined analysis of all main trials is presented in the table below.

Summary of efficacy for combined analysis of main studies

		TG (mmol/L)*		LDL-C (mmol/L)**		HDL-C (mmol/L)**	
		Coadministration	Statins	Coadministration	Statins	Coadministration	Statins
24 weeks	N	1070	1087	1070	1088	1070	1087
4 studies	Baseline	2.46	2.49	3.38	3.42	1.23	1.22
	24 weeks	1.61	2.32	3.04	3.20	1.30	1.21
	% change	-35.8	-7.4	-8.6	-5.0	6.9	0.4
Overall fixed	Treatment comparison	-29.1 (-31.5, -26.7)		-4.1 (-6.1, -2.1)		**6.4 (5.0, 7.8)**	
	P value	<0.001		Non-inferiority shown		**<0.001**	
Overall random	Treatment comparison	**-29.0 (-32.8, -25.0)**		**-5.4 (-12.7, 1.8)**		6.4 (5.0, 7.8)	
	P value	**<0.001**		**Non inferiority shown**		<0.001	
Test for heterogeneity		Q=7.50 p=0.058		Q=35.60 p<0.001		Q=2.55 p=0.467	
Adjusted for statin potency	Treatment comparison						
	Overall fixed	-		-3.4 (-5.6 ; -1.1)		-	
	Overall random	-		**-4.6 (-8.7 ; -0.5)**		-	
Test for heterogeneity		-		Q = 8.74, p = 0.033		-	
12 weeks	N	962	976	962	976	962	976
3 studies	Baseline	2.45	2.47	3.42	3.46	1.22	1.22
	12 weeks	1.66	2.29	3.19	3.20	1.31	1.22
	% change	-33.7	-9.6	-5.4	-6.1	8.1	1.2
Overall fixed	Treatment comparison	**-28.0 (-30.5 ; -25.4)**		0.04 (-1.9 ; 2.0)		6.7 (5.2, 8.1)	
	P value	**<0.001**		Non-inferiority shown		<0.001	
Overall random	Treatment comparison	-28.0 (-30.5 ; -25.4)		**-1.7 (-10.6 ; 7.2)**		**7.0 (4.5, 9.4)**	
	P value	<0.001		**Non-inferiority not shown §**		**<0.001**	
Test for heterogeneity		Q=1.73 p=0.421		Q=37.70 p <0.001		Q=5.02 p=0.081	
Adjusted for statin potency	Treatment comparison						
	Overall fixed	-		-3.6 (-6.3 ; -0.9)		-	
	Overall random	-		**-3.9 (-8.2 ; 0.5)**		-	
Test for heterogeneity		-		Q = 4.94, p = 0.084		-	

* Median values; ** Mean values; Treatment comparison consists of the difference between the LS means for coadministration and statin monotherapy with 95% CI, when presented in bold corresponds to the preferred model. § upper bound of the CI ≥ non-inferiority margin fixed at 4.0%. LDL-C statin potency drawn from [31].

Ancillary analyses

No ancillary analyses have been presented.

Summary of main studies

The following tables summarise the efficacy results from the main studies (0501 and 0502) supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). Studies 0503 and 0504 are not presented here since other statins were also administered to the tested populations.

Summary of efficacy for trial C LF0242780-01 0501

Title: A multicenter, double-blind, randomized, active comparator, forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 20 mg simvastatin alone.	
Study identifier	C LF0242780-01 05 01
Design	Multicenter phase III, randomized, double-blind, 2-parallel arm, and comparative study with a 6-week active run-in period

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks (with a simvastatin dose escalation after 12 weeks) 6 weeks 28 weeks
Hypothesis	Superiority on TG and HDL-C, non-inferiority on LDL-C at 12 weeks		
Treatments groups	Simvastatin 20 mg (simva20)		Simvastatin 20 mg taken once a day orally, during run-in of 6 weeks – 3013 patients
	Fenofibrate 145 mg + simvastatin 20 mg (feno145+simva20)		Fenofibrate 145mg + simvastatin 20 mg taken as 2 tablets, once a day orally, during 12 weeks (W0 to W12)– 526 patients randomized
	Fenofibrate 145 mg + simvastatin 40 mg (feno145+simva40)		Fenofibrate 145mg + simvastatin 40 mg taken as 2 tablets, once a day orally, during 12 weeks (W12 to W24)
	Simvastatin 40 mg (simva40)		Fenofibrate placebo + Simvastatin 40 mg taken as 2 tablets, once a day orally, during 24 weeks – 524 patients randomized
Endpoints and definitions	Primary endpoint	Change in TG, HDL-C and LDL-C (12 weeks)	Percent change from baseline to 12 weeks of treatment in TG, HDL-C and LDL-C
	Secondary endpoint	Change in TG, HDL-C and LDL-C (24 weeks)	Percent change from baseline to 24 weeks of treatment in TG, HDL-C and LDL-C
	Other secondary endpoints	Change in TC, Non-HDL-C, LDL size, ApoAI, ApoB, ApoB/ApoAI ratio, hsCRP, fibrinogen	Change from baseline to 12 weeks and 24 weeks
		Subjects reaching NCEP ATPIII targets	Percentage of subjects reaching the NCEP-ATP III targets after 12 weeks, 24, 30 and 52 weeks for LDL-C, TG, non-HDL-C, LDL-C and TG, non-HDL-C and TG, (LDL-C or non-HDL-C) and TG levels
	Safety measurement	Adverse events, withdrawals or drop-out rate, laboratory data, vital signs, physical examination	
Database lock	9 February 2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Safety subject sample: 526 in the fenofibrate 145mg+simvastatin 20/40mg (feno145+simva20/40) group and 524 in the simva40 group. Full Analysis (FA) subject sample: 493 (feno145+simva20/40) group and 505 in the simva40 group. Per Protocol (PP) subject sample: 462 in the (feno145+simva20/40) group and 459 in the simva40 group.			
Descriptive statistics and estimate variability	Treatment group	feno145 + simva20	simva40	
	Number of subject	493	505	
	TG (mmol/L) Baseline median	2.48	2.54	
	12 weeks median	1.68	2.21	

	% Change from baseline to 12 weeks median	-35.6	-12.1	
	LDL-C (mmol/L) Baseline mean (SD)	3.39 (0.66)	3.41 (0.68)	
	12 weeks mean (SD)	3.16 (0.87)	3.01 (0.83)	
	% Change from baseline to 12 weeks Mean (SD)	-5.6 (23.0)	-10.5 (23.0)	
	HDL-C (mmol/L) Baseline Mean (SD)	1.24 (0.27)	1.23 (0.30)	
	12 weeks Mean (SD)	1.32 (0.32)	1.24 (0.28)	
	% Change from baseline to 12 weeks Mean (SD)	7.3 (15.8)	1.6 (15.8)	

Effect estimate per comparison (ANCOVA with treatment, baseline value, gender and CV risk as covariate)	TG	feno145 + simva20 (LS mean estimate)	-35.26
		simva40 (LS mean estimate)	-11.96
		Treatment comparison LS mean (95%CI)	-26.47 (-29.99, -22.78)
		P-value	<0.001
	LDL-C	feno145 + simva20 (LS mean estimate)	-5.62
		simva40 (LS mean estimate)	-10.37
		Treatment comparison LS mean (95%CI)	4.75 (2.00, 7.51)
		P-value	NA*
	HDL-C	feno145 + simva20 (LS mean estimate)	8.26
		simva40 (LS mean estimate)	2.50
		Treatment comparison LS mean (95%CI)	5.76 (3.88, 7.65)
		P-value	<0.001
	*Non inferiority test with the non-inferiority on percent change in LDL-C being demonstrated if the upper boundary of the 95% CI was smaller than the non-inferiority margin fixed at 4%.		

Analysis description	**Secondary Analysis**			
Analysis population and time point description	Full Analysis (FA) subject sample: 460 in the feno145 + simva20/40 group and 469 in the simva40. Results after 24 weeks of treatment			
Descriptive statistics and estimate variability	Treatment group	feno145 + simva20/40	simva40	P value (calculated from LS mean estimate)
	Number of subject	422	437	
	TG (mmol/L) Baseline Median	2.46	2.54	
	24 weeks Median	1.58	2.26	
	% Change from baseline to 24 weeks Median	-39.0	-9.8	<0.001
	LDL-C (mmol/L) Baseline mean (SD)	3.38 (0.67)	3.40 (0.68)	
	24weeks mean (SD)	3.00 (0.90)	3.03 (0.84)	
	% Change from baseline to 24 weeks Mean (SD)	-9.7 (25.4)	-9.8 (23.0)	0.951
	HDL-C (mmol/L) Baseline Mean (SD)	1.24 (0.28)	1.23 (0.30)	
	24weeks Mean (SD)	1.32 (0.32)	1.22 (0.29)	
	% Change from baseline to 24 weeks Mean (SD)	7.4 (17.5)	0.1 (17.1)	<0.001

Summary of efficacy for trial C LF0242780-01 05 02

Title: A multicenter, double-blind, randomized study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 40 mg simvastatin alone				
Study identifier	C LF0242780-01 05 02			
Design	Multicenter phase III, randomized, double-blind, 2-parallel arm, and comparative study with a 6-week, active, run-in period			
	Duration of main phase:		24 weeks	
	Duration of Run-in phase:		6 weeks	
	Duration of Extension phase:		not applicable	
Hypothesis	Superiority on TG, LDL-C and HDL-C at 12 weeks			
Treatments groups	Simvastatin 40 mg		Simvastatin 40 mg taken once a day orally, during run-in of 6 weeks – 1187 patients	
	145 mg fenofibrate + 40 mg simvastatin (feno145+simva40 group)		Fenofibrate 145mg + simvastatin 40 mg taken as 2 tablets, once a day orally, during 24 weeks – 226 patients randomized	
	Fenofibrate placebo + 40 mg simvastatin (simva40 group)		Fenofibrate placebo + Simvastatin 40 mg taken as 2 tablets, once a day orally, during 24 weeks – 224 patients randomized	
Endpoints and definitions	Primary endpoint	Change in TG, HDL-C and LDL-C (12 weeks)	Percent change from baseline to 12 weeks of treatment in TG, HDL-C and LDL-C	
	Secondary endpoint	Change in TG, HDL-C and LDL-C (24 weeks)	Percent change from baseline to 24 weeks of treatment in TG, HDL-C and LDL-C	
	Other Secondary endpoint	Change in TC, non-HDL-C, LDL size, ApoAI, APoB, ApoB/ApoAI and,hsCRP, fibrinogen,	Change from baseline to 12 weeks and 24 weeks in hsCRP and fibrinogen	
	Secondary endpoint	Subjects reaching NCEP ATPIII targets	Percentage of subjects reaching the NCEP-ATP III targets after 12 weeks and 24 weeks for LDL-C, TG, non-HDL-C, LDL-C and TG, non-HDL-C and TG, (LDL-C or non-HDL-C) and TG levels	
	Safety measurement		Adverse events, withdrawals or drop-out rate, laboratory data, vital signs, physical examination	
Database lock	20 November 2008			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Safety subject sample: 225 in feno145+simva40 group and 224 in the simva40 group. Full Analysis (FA) subject sample: 221 in the feno145+simva40 group and 219 in the simva40group. Per Protocol (PP) subject sample: 195 in the feno145+simva40 group and 198 in the simva40 group.			
Descriptive statistics and estimate variability	Treatment group	feno145+simva40	simva40	
	Number of subject	221	219	

	TG (mmol/L) Baseline median	2.61	2.57	
	12 weeks median	1.70	2.41	
	% Change from baseline to 12 weeks median	-33.2%	-7.1%	
	LDL-C (mmol/L) Baseline mean (SD)	3.28 (0.71)	3.30 (0.73)	
	12 weeks mean (SD)	3.00 (0.83)	3.07 (0.82)	
	% Change from baseline to 12 weeks Mean (SD)	-6.3% (23.5)	-5.2% (22.0)	
	HDL-C (mmol/L) Baseline Mean (SD)	1.22 (0.27)	1.21 (0.27)	
	12 weeks Mean (SD)	1.28 (0.32)	1.19 (0.26)	
	% Change from baseline to 12 weeks Mean (SD)	5.8% (16.0)	-0.8% (13.0)	

Effect estimate per comparison (ANCOVA with treatment, baseline value, gender and CV risk as covariate)	TG	Feno145 + simva40 (LS mean estimate)	-35.062
		Simva40 (LS mean estimate)	-9.570
		Treatment comparison LS mean (95%CI)	-28.19 (-32.91, -23.13)
		P-value	<0.001
	LDL-C	Feno145 + simva40 (LS mean estimate)	-7.731
		Simva40 (LS mean estimate)	-6.487
		Treatment comparison LS mean (95%CI)	-1.24 (-5.22, 2.73)
		P-value	0.539
	HDL-C	Feno145 + simva40 (LS mean estimate)	7.296
		Simva (LS mean estimate)	0.834
		Treatment comparison LS mean (95%CI)	6.46 (3.83, 9.09)
		P-value	<0.001

Analysis description	**Secondary Analysis**			
Descriptive statistics and estimate variability	Treatment group	feno145+simva40	Simva40	P value (calculated from LS mean estimate)
	Number of subject	213	203	
	TG (mmol/L) Baseline median	2.61	2.54	
	24 weeks median	1.76	2.56	

	% Change from baseline to 24 weeks median	-30.9	-4.1	<0.001
	LDL-C (mmol/L) Baseline mean (SD)	3.27 (0.71)	3.30 (0.74)	
	24 weeks mean (SD)	3.08 (0.86)	3.34 (1.01)	
	% Change from baseline to 24 weeks Mean (SD)	-4.0 (24.16)	3.1 (30.0)	0.005
	HDL-C (mmol/L) Baseline Mean (SD)	1.22 (0.27)	1.22 (0.27)	
	24 weeks Mean (SD)	1.28 (0.30)	1.22 (0.28)	
	% Change from baseline to 24 weeks Mean (SD)	5.1 (16.1)	0.6 (13.2)	0.001

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

In the integrated analysis of the four studies analysed at 12 weeks, fenofibrate 145 mg + simvastatin 20 mg only reached the TG and HDL-C objectives of superiority over statin monotherapy with similar incremental changes, 28.0 % and 7.0%, respectively. A highly statistically significant heterogeneity was observed between studies for LDL-C. Thus, the additional 1.7% reduction in LDL-C at 12 weeks with co-administration as compared with statin monotherapy had a 95% confidence interval which crossed the 4% non-inferiority margin with the random model. Analysis at 24 weeks showed that fenofibrate 145 mg + simvastatin 40 mg reached its three objectives, superiority on TG and HDL-C and non-inferiority in LDL-C, thus fulfilling the pre-defined hypothesis of efficacy. When compared to statins, co-administration of fenofibrate 145 mg and simvastatin 40 mg gave an additional reduction in TG by 29.0%, an additional increase in HDL-C by 6.4% and an additional reduction in LDL-C by 5.4% (95%CI -12.7; +1.8%).

Clinical studies in special populations

Within the development programme, certain special or sub-populations were studied and these included subjects with renal impairment, subjects older than 65 years and women. Although the studies were not specifically designed to investigate these subgroups, the distribution of patients made subgroup analysis possible. In the group with renal insufficiency (n=204), comparison of subsets based on their eGFR (30-59mls/min/1.73m2 or ≥ 60 mL/min/1.73m²) the incremental reduction of TGs and increase of HDL were both were higher in the FDC group as compared with simvastatin alone group. There were no subjects with eGFR <30ms (an exclusion criterion) and therefore no conclusion can be drawn. Gender was another criteria where showed a consistent interaction with treatment although these data were generated within the main studies and not by specific gender based studies. The treatment by gender interaction suggests that the fixed dose combination has less effect in males but this finding remains to be fully explained. In light of the beneficial effects on biochemical parameters in both males and females this lack of understanding is not considered reason for objection.

Supportive studies

The applicant presented the results of several published studies in support of the application in the dossier. Of these, the large long-term ACCORD study is discussed in detail and the FIELD trial in diabetic patients is referenced for safety aspects. Whilst the therapeutic indication claimed for Cholib relates to biochemical parameters (TG, HDL-C and LDL-C), discussion is also provided on the clinical outcome data of the ACCORD and FIELD trials, please see table below. The supportive studies include basis for use of fenofibrate in specific populations but with marginal benefit in terms of clinical events overall. The ACCORD study results do not achieve statistical significance to support the use of the combination in all patients and results are stronger in specific subgroups of patients. With respect to the FIELD study, specifically regarding the diabetic patients who are the main group with mixed dyslipidemias and deemed high risk, the results/outcomes were not convincingly different between fenofibrate and placebo groups, and any difference noted was primarily in re-vascularisation. Importantly, this was treatment with fenofibrate alone and not the combination.

In terms of clinical outcomes, these two published studies provide strong data supporting the use of the statin + fenofibrate combination in a subset of the high risk patient group. The net gain in different published studies of the co-administration or incremental doses of statins is clearly in favour of incremental doses of statins. There is evidence of incremental benefit with statins (without fenofibrate) especially on LDL-C level and to an extent even on TGs and HDL-C levels, emphasising the need to demonstrate any advantages of the FDC in terms of clinical events over the standard clinical guideline and practise recommendations to optimise the dose of statins in all high risk subjects before additional treatments are considered.

Overview of main results obtained in the supportive efficacy studies

Efficacy of the Coadministration of Fenofibrate/Fenofibric Acid and Statins (Simvastatin, Atorvastatin and Rosuvastatin)

Study	Treatment Duration Study Design	Population	No of Subjects Analyzed	Fenofibrate Dosage (mg)	Statin Dosage (mg)	Modification of Lipid and Apolipoprotein Levels (%) Compared to Baseline (After Statin-Run in Pivotal Studies; Without Treatment in Other Studies)					
						TG	LDL-C	HDL-C	Non HDL-C	Apo B	Apo B/A1 Ratio
ACCORD lipid 2007 and 2010	5 years Rando, DB, PG (2 arms) vs. simvastatin	T2DM	2287	F160	S20/40	-22	-19	+8	-	-	
			2271	-	S20/40	-9	-21	+6			
Goldberg 2009	3 months Rando 2:2:2:2:2:1, DB, PG (6 arms)	Mixed dyslipidemia	105	FA135	A20	-46	-34	+14	-41	-37	
			102	FA135	A40	-42	-35	+13	-43	-37	
			104	FA135	-	-30	-3	+20	-15	-12	
			109	-	A20	-17	-37	+6	-36	-33	
			105	-	A40	-23	-40	+5	-42	-35	
			52	-	A80	-30	-46	+6	-45	-40	
Jones 2009	3 months Rando, 2:2:2:2:2:1 DB, PG (6 arms)	Mixed dyslipidemia	252	FA135	R10	-47	-37	+20	-45	-39	
			249	FA135	R20	-43	-39	+19	-45	-39	
			242	FA135	-	-33	-7	+15	-19	-16	
			252	-	R10	-24	-38	+9	-40	-34	
			255	-	R20	-26	-45	+10	-46	-40	
			127	-	R40	-32	-51	+9	-52	-45	

Abbreviations: A atorvastatin; DB: Double-blind; Eze: ezetimibe10 mg; F: fenofibrate; FA: Fenofibric acid; NCEP National cholesterol education program; PG: parallel-group; R Rosuvastatin; Rando: randomized; S simvastatin

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme for Cholib was conducted with the co-administration of fenofibrate and simvastatin. Four main clinical studies were carried out, which were supported by five published double-blind supportive studies with fenofibrate or fenofibric acid and simvastatin (these also include the long-term studies FIELD and ACCORD lipid). All pivotal studies were double blind, randomised, active controlled studies with trials 0501 and 0503 adopting a forced titration for simvastatin dose. The studies investigated a single dose of fenofibrate, which can limit the potential to evaluate a true dose response. All subjects were first included in a 6-week open-label run-in period with statin monotherapy. Subjects not adequately controlled by statin were randomised in a 24-week double-blind period (DB) using the run-in statin as the control treatment. In all studies except the 0502 study, the subjects who completed the double-blind period entered a 28-week open-label extension period (OP).

The study participants are considered broadly representative of the population that the applicant aims to seek the indication for, although the patients included in the clinical trials did not have LDL-C control at baseline, thus representing a more rigorous experimental situation for the examination of the simvastatin component. A group of patients with mixed dyslipidemia (type-2 diabetes mellitus) were excluded from the pivotal trials, though were included in the long term studies with fenofibrate, such as ACCORD lipid and FIELD trials. The exclusion of the population

with diabetes, the most common single disease with mixed dyslipidemia at high risk of CV events, from the pivotal studies is a limitation of this development programme, though as indicated, data in this subset of the population are included in the large supportive studies. Therefore reliance is placed on publications and the data presented there as evidence in such patients; appreciating that both of the monocomponents, used alone or in combination, are used in this population in clinical practice. In addition, in the context of the restricted indication, extrapolation from the trial population across the different types of patients who have LDL-C control on simvastatin when switching to the fixed dose combination is reasonable and the exclusion of this group from the clinical trial population presents no objection.

The objectives of the pivotal studies are well defined in terms of the effects on biochemical parameters: a reduction in TGs, reduction in LDL-C and increase of HDL-C. The blinding, randomisation and study evaluation are considered appropriate for the endpoints. The ideal design here would have included a monotherapy arm with incremental doses of simvastatin or ensure to that the run in statin was appropriately dosed. Whilst this is not considered to be a critical issue by the CHMP, since the studies still represent a rigorous examination of the efficacy of the simvastatin component, there is no definitive answer on further titration of simvastatin compared to the addition of fenofibrate. Nevertheless, this is a matter for clinical practice and therapeutic choice, and does not directly bear on the assessment of risk-benefit for the fixed dose combination. The methods used to analyse the data include the stratification factors used in the randomisation and are considered adequate by the CHMP. The method used to handle the missing data is acceptable since the amount of missing data is relatively small. The control of the Type I error is appropriate. The margin chosen to demonstrate non-inferiority has not been comprehensively justified and reasoned, nonetheless whilst this complicates a formal conclusion the estimated effects and associated confidence intervals can still be interpreted for their clinical relevance. The objective, endpoints proposed in support of the biochemical effects, blinding and randomisation are satisfactory. The overall clinical aim of the treatment is to gain and maintain control of lipids to reduce residual CV risk. It is of interest therefore to reflect on whether the reduction of TGs and increasing HDL-C levels that are beneficially impacted by adding the fibrate component translates into clinical event reduction. This is yet to be fully established as reflected in the CHMP guideline on lipid modifying agents, which states that surrogacy is applicable to LDL-C levels and mainly to statins. However, the therapeutic indication agreed concentrates on the effects on the biochemical parameters and a definitive answer to this question is not critical to judge the risk-benefit in the proposed indication; the use of the medicine is a matter for clinical practice. The key for this dossier is to establish that there are clinical data to ensure the maintenance of the LDL-C levels in patients who switch from simvastatin alone to the fixed dose combination in light of the reduction in exposure to the active metabolite of simvastatin and any resulting reduction of effect on LDL-C, a well-accepted surrogate for CV benefit with statins.

Efficacy data and additional analyses

The main clinical outcomes in the trials were changes in lipid parameters in the 12 and 24 week observations. The CHMP noted that no long-term data in terms of clinical outcomes were presented and this can be accepted in light of the reference to biochemical parameters and not to clinical outcomes in the therapeutic indication.

The main difference between the combination arm and the statin alone arm in each study is in the reduction of TGs and increase in HDL-C. This finding routinely achieves statistical significance

validating the efficacy of the fibrate component administered concomitantly with the statin. In the pooled primary variable analysis, the evidence for greater reduction of TG and higher percentage point increment to HDL-C levels has been demonstrated. The effect of the fibrate component is established.

With regards to the LDL-C levels, the reductions in LDL-C of 0.8% and 3.4% at 12 and 24 weeks respectively, in a combined analysis of all studies (0501-0504) falls short of an 'additive' effect of the two components if one considers the expected margins of LDL-C reduction with each agent in monotherapy (~27-34% for simvastatin *vs* 15-30% for fenofibrate). There is an interaction between treatment and gender for LDL-C in more than one of the clinical studies, impacting interpretation of the results, in terms of understanding the overall estimated effect. From a statistical view point, study 0501 did not formally demonstrate non-inferiority for LDL-C. In study 0502, the same complications with respect to missing data and interpretability of results considering the failed primary endpoint remain for this study

As regards the gender differences previously noted by the CHMP, more analysis of ACCORD, FIELD publications and the lately conducted phase-1 study (PK- PD effect between genders at 7 days) were presented. The applicant argued that treatment by gender interaction for the primary outcome in ACCORD lipid trial is not consistent with other studies with fenofibrate, including FIELD, in which there was no significant treatment-by-gender interaction and estimates of the fenofibrate treatment benefit were numerically larger in women than in men. In the population who should benefit more from the combination, high risk patients with controlled LDL-C on statin monotherapy, there was a reduction in CV events with co-administration of fenofibrate and simvastatin overall with no harm in women. The treatment by gender interaction finding remains to be fully explained, but in light of the beneficial effects on biochemical parameters in both males and females this lack of understanding is no reason for objection.

Studies 0503 and 0504 are considered 'supportive' rather than pivotal studies in light of the proposed indication to use the product in patients with LDL-C control on simvastatin, which hence becomes the comparator of primary interest. Studies 0503 and 0504 used different control arms and they no longer bear directly on the proposed indication. They do however offer supportive evidence in terms of the effect of Cholib on LDL-C. The FDC has less effect on the LDL-C reduction compared to the dose of atorvastatin either at 12 or 24 weeks as observed in study in 503, but in particular considering the limited indication proposed, the relative potency between different doses of statins is of no concern. PD measurements included in the study in healthy volunteers (M13-953) are also supportive, despite being short term. A further post-hoc analysis of the ACCORD data based on the publication was presented by the applicant emphasising the subgroup analysis in the dyslipidaemic population as identified using the NCEP criteria. A similar analysis from FDA review group was also included, which used a different cut-off for TG levels. These analyses suggest that in that subgroup there was a difference in CV events in favour of the simvastatin plus fenofibrate in comparison to statin monotherapy. In ACCORD lipid trial, the patients within the high risk diabetic population remaining dyslipidaemic on statin therapy with controlled LDL-C levels, with high TG and low HDL-C benefited from a significant reduction in the primary endpoint with a satisfactory safety profile over 5 years. In total, the clinical data confirm that any impact of the pharmacokinetic interaction between fenofibrate and simvastatin has a clinical impact that is not relevant and the effect of simvastatin on LDL-C levels is observed in the clinical trials.

A formal conclusion of non-inferiority for the effect on LDL-C levels in a population of patients who are not well controlled on simvastatin is not possible. This was the target population that was originally proposed. On request of the CHMP, the applicant restricted the indication to use this combination in those patients for whom the LDL-C was controlled by the corresponding dose of simvastatin:

"Cholib is indicated as adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase HDL - C levels when LDL - C levels are adequately controlled with the corresponding dose of simvastatin monotherapy."

For the revised target population based on patients who are already controlled on simvastatin, the formal failure of the studies cannot be regarded so critically in light of clear effect on LDL-C levels as expected from simvastatin 20 and 40mg, the clinical pharmacology data and the supportive clinical data that are described above. For this indication, there is clear evidence in the clinical trials for a beneficial effect of the fibrate component on biochemical parameters of HDL-C and TG levels and the weight of evidence from the multiple clinical trial publications presented indicates that control of LDL-C can be expected to be maintained from the simvastatin component. Whilst the substance interaction that decreases exposure to LDL-C is of some concern, it appears to be of similar magnitude to that observed for the temporally dissociated free association and evidence from the ACCORD study publication, larger than the pivotal studies presented, indicates control of LDL-C, albeit in a different patient population.

2.5.4. Conclusions on the clinical efficacy

The applicant has presented a clinical rationale for each strength of the proposed fixed dose combination, noting the established role of statins in reducing CV risk and CV events and lack of difference in clinical outcome between "more statins *vs* less statins" using the SEARCH and IDEAL trials. It is accepted that simvastatin is licensed at the doses proposed and these doses are used in clinical practice in the treatment of high risk patients using the lower strength in order to achieve control of LDL-C, or due to problems tolerating higher doses or more potent statin treatment. If a patient has control of LDL-C based on simvastatin 20mg and the treating physician elects to add a fibrate for effects on TG and HDL-C, then the fixed dose combination represents a viable treatment option.

In light of the proposed change to the therapeutic indication it is considered that the efficacy for Cholib has been demonstrated. The change to the indication mitigates the methodological concerns described above and the totality of evidence is reassuring such that not only will the fibrate component benefit HDL-C and TG levels, but efficacy on LDL-C will be maintained by the combination. Residual concerns related to the substance interaction, on which further information was provided in M13-963 study indicating that the interaction was no greater than for the temporally dissociated free association. Long-term data from ACCORD provide reassurance that simvastatin can exert its effect on LDL-C in the presence of fenofibrate and hence despite the presence of the pharmacokinetic interaction although no difference in mean LDL-C levels were noted in the two arms possibly suggesting that interaction did not influence mean LDL-C levels. The CHMP considered that the interaction was sufficiently small not to detrimentally affect the risk level if the combination is aimed at a population that had already established LDL-C control.

2.6. Clinical safety

The overall safety of the fixed dose combination is based on data from 3 different sources; i) the clinical and laboratory safety in the pivotal studies; ii) data from supportive studies with co-administration of fenofibrate and simvastatin, and iii) additional supportive data provided by studies in the same populations as mixed dyslipidemia with co-administration of fenofibric acid with other statins, atorvastatin and rosuvastatin. The evaluation of safety is based on the comparison of co-administration and statin monotherapy during the 24-week randomized treatment period. As the pivotal trials used very similar designs, the results of integrated pre-defined safety evaluation plan are expected to provide the framework. The adverse events of special interest are muscle, renal and hepatic events. The observations made during the 28-week extension period permit one to get insights into the safety profile of co-administration for up to one year.

Patient exposure

The exposure in the double blind phase is described in the tables below.

Extent of Exposure - From Baseline to 24 Weeks

Extent of Exposure	Statistic	DB Feno 145 + Simva 20/40 (N=1204)	DB Statins (N=1194)
< 6 weeks	N (%)	24 (2.0)	30 (2.5)
>= 6 weeks	N (%)	1180 (98.0)	1164 (97.5)
>= 12 weeks	N (%)	1132 (94.0)	1135 (95.1)
>= 24 weeks	N (%)	803 (66.7)	797 (66.8)

Overall exposure of subjects

	Baseline - 24 Weeks of Treatment		Baseline - 12 Weeks of Treatment	
Exposure (days)	Feno 145 + Simva 20/40 (N=1204)	Statins (N=1194)	Feno 145 + Simva 20/40 (N=1237)	Statins (N=1230)
Mean (SD)	160.3 (32.5)	161.5 (31.9)	83.6 (11.9)	83.2 (12.9)
Median	168.0	168.0	84.0	84.0
Min/Max	4 / 238	1 / 272	4 / 124	1 / 160

The 1,602 subjects entering the open extension period were subdivided into 786 initially randomized to co-administration and 816 initially randomized to statin monotherapy. Thus, 2,053 subjects (1,237 + 816) received the co-administration; 979 coming from the three studies with a 28-week open extension were exposed to up to 52 weeks and were analysed for the period from baseline to 52 weeks. The overall exposure of subjects in the clinical development programme of Cholib is considered acceptable to the CHMP.

Adverse events

The summary distribution of treatment-emergent adverse events (TEAEs) in the four studies of the clinical program is shown in the table below.

Overall summary of AEs

Summary of Adverse Events

Baseline-24 weeks	Coadministration F145/S20-40 (N=1204)		Statins (N=1194)	
	Subject	Event	Subject	Event
At least one TEAE	528 (43.9%)	846	494 (41.4%)	818
At least one related TEAE	162 (13.5%)	204	136 (11.4%)	198
At least one TESAE	44 (3.7%)	51	44 (3.7%)	49
At least one related TESAE	6 (0.5%)	7	3 (0.3%)	3
TE deaths	5 (0.4%)*	5	3 (0.3%)	3
Baseline-12 weeks	**Coadministration F145/S20-40 (N=1237)**		**Statins (N=1230)**	
	Subject	**Event**	**Subject**	**Event**
At least one TEAE	280 (22.6%)	386	265 (21.5%)	383
At least one related TEAE	86 (7.0%)	100	78 (6.3%)	103
At least one TESAE	26 (2.1%)	29	27 (2.2%)	30
At least one related TESAE	3 (0.2%)	3	2 (0.2%)	2
TE deaths	3 (0.2%)	3	1 (0.1%)	1

*: One additional subject died 20 days after discontinuation of treatment. TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event, TE: treatment-emergent.

The frequency of AEs did not differ between the combination co-administration and statin monotherapy in any study but differed between studies: lowest in study 0503 (approx. 20% for each 12 week period) and highest in study 0502 (approx. 33%). There was a relationship between dose and frequency of adverse events in both the 12- and 24-week analyses with the higher dose having higher event rates, although the difference was not statistically analysed. During the open-label run-in period, the percentage of subjects who experienced at least one AE was higher for the non-randomised subjects (32.0% of subjects) compared to the randomised group (20.3% of subjects). Overall, 8.4% of the non-randomised subjects experienced at least one AE leading to study termination. Sudden death occurred in one subject during the run-in period in study 0501.

During the entire co-administration treatment period, 62.9% of the subjects treated with fenofibrate 145mg + simvastatin 20/40 mg co-administration reported at least one TEAE (TEAE related to study treatment for 23.0% of subjects), 6.7% of the subjects experienced at least one TESAE (related TESAE for 1.0% of subjects) and 14.0% of the subjects discontinued the study because of TEAEs. The frequency of different adverse events has been coded based on the system organ class and preferred term. There were 10.1% of subjects in the co-administration group who reported AEs that classified as possibly and probably treatment related. This figure was 7.5% in the statin monotherapy group. Four events were reported with a frequency of >2% cut-off (predefined in the integrated analysis of safety) for the double blind period: increases in creatinine, in C-reactive protein (CRP), in Gamma Glutamyl Transferase (GGT), and in fasting glucose. The increase in creatinine was more frequent in the co-administration group, whereas increases in CRP and fasting glucose were more frequent in the statin monotherapy group. The comparison in the below table demonstrates that the difference between the patients randomised and non-randomised to statins.

Adverse events by SOC in the run-in period.

Description of Adverse Events by SOC in the Statin Run-in Period

	Randomized (N=2474)		Not Randomized (N=5109)		Total (N=7583)	
	S	E	S	E	S	E
Blood and lymphatic system disorders	7 (0.3%)	7	17 (0.3%)	17	24 (0.3%)	24
Cardiac disorders	7 (0.3%)	7	24 (0.5%)	25	31 (0.4%)	32
Ear and labyrinth disorders	3 (0.1%)	3	3 (0.1%)	3	6 (0.1%)	6
Endocrine disorders	0		63 (1.2%)	64	63 (0.8%)	64
Eye disorders	2 (0.1%)	2	3 (0.1%)	3	5 (0.1%)	5
Gastrointestinal disorders	20 (0.8%)	21	78 (1.5%)	92	98 (1.3%)	113
General disorders and administration site conditions	2 (0.1%)	2	25 (0.5%)	26	27 (0.4%)	28
Hepatobiliary disorders	4 (0.2%)	5	21 (0.4%)	22	25 (0.3%)	27
Immune system disorders	1 (0.0%)	1	4 (0.1%)	4	5 (0.1%)	5
Infections and infestations	43 (1.7%)	44	55 (1.1%)	56	98 (1.3%)	100
Injury, poisoning and procedural complications	11 (0.4%)	11	11 (0.2%)	11	22 (0.3%)	22
Investigations	374 (15.1%)	447	1280 (25.1%)	1730	1654 (21.8%)	2177
Metabolism and nutrition disorders	3 (0.1%)	4	116 (2.3%)	118	119 (1.6%)	122
Musculoskeletal and connective tissue disorders	26 (1.1%)	30	53 (1.0%)	61	79 (1.0%)	91
Neoplasms benign, malignant and unspecified	1 (0.0%)	1	2 (0.0%)	2	3 (0.0%)	3
Nervous system disorders	14 (0.6%)	14	28 (0.5%)	33	42 (0.6%)	47
Psychiatric disorders	4 (0.2%)	4	7 (0.1%)	8	11 (0.1%)	12
Renal and urinary disorders	6 (0.2%)	7	17 (0.3%)	17	23 (0.3%)	24
Reproductive system and breast disorders	2 (0.1%)	2	4 (0.1%)	4	6 (0.1%)	6
Respiratory, thoracic and mediastinal disorders	4 (0.2%)	4	7 (0.1%)	8	11 (0.1%)	12
Skin and subcutaneous tissue disorders	7 (0.3%)	7	21 (0.4%)	22	28 (0.4%)	29
Surgical and medical procedures	3 (0.1%)	3	4 (0.1%)	4	7 (0.1%)	7
Vascular disorders	10 (0.4%)	10	11 (0.2%)	11	21 (0.3%)	21

S: N (%) of subjects; E: N of events.

Serious adverse event / deaths / other significant events

Serious adverse events

The reporting of serious AEs was based on the different periods, however, the following observations can be made: In the run in period (with statins), SAEs were reported in 14 randomized subjects (0.6%) and 46 non-randomized subjects (0.9%) but without a meaningful difference between groups and majority were due to laboratory abnormalities.

On hundred treatment emergent serious adverse events (TESAEs) were reported during the 24-week double blind period with an overall frequency of 3.7% in both treatment groups. The organ distribution of these serious events was similar across the groups. Between baseline and 24 weeks, 44 subjects (3.7%) experienced a TESAE in the co-administration group and 44 subjects (3.7%) in the statins groups. The most common TEAE were cardiac disorders (1.2%) mainly myocardial infarction and angina pectoris along with liver function abnormalities. The incidence of cardiac disorders (MI or angina) did not differ between groups and in the statin monotherapy group; surgical disorders in 11 subjects were the most common AEs (mainly knee arthroplasty of hip surgery).

In the open extension period, 4.1% subjects (n=66) subjects experienced TEAEs. In the low dose group (fenofibrate 145mg + simvastatin 20mg), the most commonly observed were laboratory abnormalities (including increased transaminases). In the fenofibrate 145mg + simvastatin 40mg subgroup, the most common TESAEs occurring between 24 and 52 weeks were cardiac disorders (11 subjects, 0.9%), common ones being angina and acute MI. Nine subjects experienced eight TESAEs considered as related to study treatment by the investigator (one necrotizing pancreatitis, one gallbladder empyema, two increased CK, one metastatic disease, one acute renal failure, one pleural effusion, one pulmonary embolism).

Deaths

There were 14 deaths in this clinical programme with 2474 patients randomised into the double blind 24 week treatment period and 1602 receiving the combination (co-administration) in the 28 weeks open extension period;

- Nine deaths during the double blind treatment period (4 fatal CV events, 3 sudden deaths, one road traffic accident and one homicide); of these 6 were in the co-administration group (0.5%) and 3 were in the statin monotherapy group(0.3%)
- Four subjects died during the open extension period (one each of sudden death, rupture of abdominal aortic aneurysm, suicide and unknown cause).

None of these deaths were considered to be related to the study drugs. There were four deaths in study 0501, two in 0502, four in 0503 and four in 0504. Narrative descriptions of these have been included.

AEs of special interest

The grouping of AEs by standardized MedDRA queries did not seem to result in identifying potential risk for muscle, renal and hepatic adverse effects beyond what would be expected based on the respective risks of fenofibrate and simvastatin monotherapies. For muscle effects, the standardized query showed a frequency of 2.2% in the co-administration group and 1.9% in the statin monotherapy group with only three serious events in total. Myalgia was the most commonly reported muscular AE although its frequency was below 2%. Other muscular signs/symptoms were uncommon. No cases of rhabdomyolysis were reported. A difference was noted between co-administration and monotherapy groups for renal effects with a frequency of 10.1 % *vs* 4.6%, respectively. The increase in creatinine levels which was predefined to be reported as AE with two elevations from baseline by 30µmol/L or more was the most common AE (10.0% in the co-administration group and 4.4% in the statin monotherapy group). Hepatic disorders showed a frequency of 5.4% in the co-administration group and 5.9% in the statin monotherapy group, with seven serious events in total. There was no case of concomitant increase in transaminase and total bilirubin levels above 1.5×ULN indicative of potentially severe liver necrosis. The most common hepatic disorder was increased GGT observed in 3.7% of subjects with co-administration and 3.5% with statin monotherapy, followed by increase in total bilirubin levels, which had incidence two times higher with statin monotherapy than with co-administration.

Laboratory findings

The laboratory findings or abnormalities formed the commonest AEs especially in the run-in period and was higher in the non-randomised group overall. The important or common laboratory abnormalities were elevation of creatinine kinase (CK) enzyme, elevated transaminases (AST and ALT) and lastly elevated plasma/serum creatinine values. The CK elevation >10×ULN were infrequent in the clinical programme with an upper limit of 95% confidence interval of its frequency below 1% in either treatment period. Increase >5xULN was noted in 1.5% but did not differ between groups. The AST elevation >3xULN occurred with the same frequency across groups but differed marginally between treatment periods. Elevations of ALT>3xULN were twice as common with the co-administration during the DB period as compared with statin monotherapy. Cases of transaminase elevation >5×ULN were infrequent with an upper limit of 95% CI not exceeding 1.1%. None of these cases were associated with concomitant elevation of total bilirubin.

Elevation of creatinine is of some interest and is an expected phenomenon with fenofibrate, as it was observed in the previous fenofibrate trials including ACCORD lipid and FIELD trials. The mean creatinine level increased after the first six weeks of co-administration (as expected for fenofibrate) and remained approximately 8 µmol/L higher than with statin monotherapy. In the open extension period, the transition from statin monotherapy to co-administration of fenofibrate and simvastatin induced the same shift in creatinine levels six weeks later, whereas creatinine levels remained in plateau when co-administration was continued. Except for two cases in the open extension phases, none of these cases resulted in acute renal failure. Creatinine levels of 177µmol/L or higher were measured in 22 cases (0.3%) during statin run-in, 19 cases (0.8%) during the double-blind period (including 13 cases (1.1%) with co-administration and six cases (0.5%) with statin monotherapy) and 18 cases (1.1%) during the open extension period. Interestingly, creatinine and ALT elevations appeared to be related to gender (more in females) in both co-administration and monotherapy groups during the double blind period. Based on the FIELD study results, slightly larger increments in creatinine levels (10-12 µmol/L) was maintained over 5 years on treatment with fenofibrate. This shift was not considered to be associated with harm.

Safety in special populations

In this phase 3 programme, there are no data available for subjects with hepatic dysfunction or paediatric populations.

Increases in creatinine levels, defined in the protocol as increase from baseline by 30µmol/L or more, were more frequent in subjects aged 65 years or above in each assigned treatment group; the frequency was higher in those with reduced eGFR. Patients with significant renal disease were excluded and patients with mild to moderate renal disease were included in the original clinical studies. Therefore, the use of Cholib in patients with severe renal impairment is contraindicated and dosing recommendations are given in the SmPC for patients with mild to moderate renal impairment.

There were no meaningful differences in GGT, CRP and glucose elevation between subpopulations.

Safety related to drug-drug interactions and other interactions

The applicant has taken the view that all interactions listed in the product literatures of the two active substances/monotherapies are applicable and as these products are established in clinical use, it was considered that new interaction studies were not required. Accordingly, the proposed product label includes most of the interactions listed for both agents. The RMP adequately details the interaction related actions and activities proposed for risk minimisation.

Of interest is the interaction between fenofibrate and simvastatin, resulting in approximately 40% reduction in AUC of simvastatin acid. This issue and its potential unfavourable effect on the overall benefit/risk of Cholib are discussed in the section on Pharmacokinetic drug interactions.

Discontinuation due to adverse events

The overall rate of discontinuations for any AE was higher with co-administration (7.2% with co-administration and 3.8% with statin monotherapy). The most common reason was found in the SOC Investigations (3.8% with co-administration and 1.3% with statin monotherapy) followed by the SOC Gastrointestinal Disorders (0.9 % with co-administration and 0.6% with statin monotherapy). The most frequent PT mentioned as reason for discontinuation was increased creatinine levels (3.2 % with co-administration and 0.8% with statin monotherapy) followed by myalgia (0.6% in each treatment group). The two-time higher frequency of discontinuations with co-administration was driven by withdrawal for PT Increased creatinine, whereas the rate of discontinuations for PTs Increased creatine kinase (CK), myalgia or HLT liver function test analysis (LFTs) were below 1%.

Post marketing experience

There is currently no post marketing experience with Cholib, since it has not been marketed yet.

2.6.1. Discussion on clinical safety

The safety of fenofibrate and simvastatin co-administration is based on the analyses of:

- four double-blind studies which randomized 2,474 subjects with mixed dyslipidemia at high risk of cardiovascular disease to co-administration of fenofibrate 145 mg and simvastatin 20 to 40 mg for up to six months, with a follow-up to one year of 979 of these subjects,
- five double-blind studies of three months to one year duration using fenofibrate or fenofibric acid in 2,420 subjects with mixed or combined hyperlipidemia,
- safety databases over the 10-year period 1998-2007 with regard to muscle, renal and hepatic AEs,
- the ACCORD lipid study in 5,518 patients with type 2 diabetes mellitus with administration of fenofibrate and simvastatin or simvastatin monotherapy for an average 5-year follow-up.

The overall exposure of subjects is considered acceptable for the proposed therapeutic indication. Most of the premature study withdrawals were due to clinical or laboratory TEAEs, e.g.

consecutive elevations of creatinine levels (>30µmol/L) from baseline. In general, the adverse events rates were higher for the combination (fenofibrate/simvastatin) in comparison with statin monotherapy. A relationship with the dose was observed with fenofibrate 145mg/simvastatin 40mg showing numerically higher AEs than the fenofibrate 145mg/simvastatin 20mg co-administration. Overall, the frequency of TEAES was approximately 63% over the year. There are differences between studies in the reporting of AEs and this is likely to be related, amongst other factors, to the statin used. The common adverse events described here have been known and recognised before. The data set does not indicate significant differences in AEs of special interest in the two groups, except for increased creatinine and increase ALT. These findings are of interest in patients with kidney and liver impairments, but the difference between monotherapy and co-administration is small. Adequate advice has been included in the SmPC of Cholib. The findings in relation to muscle disorders showed no difference between the co-administration of fenofibrate and simvastatin and the use of simvastatin alone, which is reassuring. The frequency of TESAEs was not concerning in either the double blind or the open extension periods. In the DB periods, the two groups did not differ significantly. The number of deaths is not of concern. Small differences between groups within the 4 studies were noted but none could be ascribed causally to the study drugs. This finding is unsurprising and given that the population was at high risk of CV events, these differences are not considered relevant.

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

2.6.2. Conclusions on the clinical safety

The overall safety profile of co-administration of fenofibrate and simvastatin is considered acceptable. The adverse events specific to the sub-population with impaired renal and/or hepatic function are captured in the SmPC of Cholib and adequately inform the prescribing physicians. There is a potential under-detection/under-reporting of muscle symptoms but this is not considered to be a major concern due to the extensive use and knowledge of the two agents. The issues relating to identification of risk and risk minimisation are satisfactorily addressed in the RMP. The interaction between simvastatin and fenofibrate with resultant reduction in AUC of simvastatin acid by around 40% was addressed. Namely, the applicant attempted to resolve the impact of this on the long-term effects of simvastatin, and address whether there is a potential for mitigation of the expected benefits of simvastatin in the high risk population purely due to the administration of the FDC, in part by demonstrating that the interaction is present to an apparently similar degree for the free association administered at different times. The ACCORD study provides further supportive information to address the residual concerns and the applicant mitigates the risk by restricting the therapeutic indication, which is considered acceptable and is agreed by the CHMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

the legislative requirements.

2.8. Risk Management Plan

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

The PRAC considers by consensus decision that the risk management system for the fixed dose combination of fenofibrate and simvastatin (Cholib) is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Cholelithiasis Pancreatitis Myopathy/Rhabdomyolysis Drug-induced hepatitis Elevations in serum creatinine Photosensitivity Venous thromboembolic disease New onset diabetes mellitus and hyperglycaemia
Important potential risks	Increased risk of Major Adverse Cardiac Events in women on combined treatment Off-label use (in particular, initial prescription in naïve patients) Increased blood homocysteine levels
Missing information	Children/adolescents (< 18 years) Pregnant/lactating women Patients with severe renal impairment Patients with hepatic insufficiency

- **Pharmacovigilance plans**

Activity / Study title	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Drug Utilisation Study (Category 3)	To assess how the product is used in clinical practice to ensure the labelling measures are sufficient to ensure	Off-label use (in particular, initial prescription in naïve patients)	Planned	Regular updates will be provided in PSURs

Activity / Study title	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	appropriate use			
Randomized, double-blind, placebo-controlled clinical trial (Category 3)	Confirmation of a potential signal identified in subgroup analyses of ACCORD Lipid data, and of any clinical consequences thereof	Increased Risk of Major Adverse Cardiac Events in Women on Combined Treatment	Planned	Final study report 31/01/2021

- **Risk minimisation measures**

The PRAC, having considered the data submitted, was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The proposal to use a combination of fenofibrate and a statin in individuals at high CV risk who respond adequately to simvastatin monotherapy in terms of LDL-C and do not reach NCEP-III lipid goals for TGs and HDL-C change is justified in that low HDL-C has been noted to impact the residual CV risk in those subjects with mixed dyslipidemias. The clinical development programme aimed to achieve reduction in TGs and an increase in HDL-C in a population that has received simvastatin at a given dose. Four specific pivotal trials were conducted comparing the combination of fenofibrate and simvastatin with different statins in order to have consolidated dataset that could prove the value of the fenofibrate+simvastatin combination in two dosage strengths.

In all studies, the aim of reducing TGs significantly was achieved. This was greater with the combination (FDC or coadministered fenofibrate +simvastatin) than with the comparator statin (simvastatin in 0501 & 0502, atorvastatin in 0503 and pravastatin in 0504). The change in HDL-C with the combination was also greater than the statin alone in 0501, 0502 and 0504. Other secondary end points also showed reduction (non-HDL-C, Apo B, Apo-A1 and Apo AII, etc). Thus, the beneficial effect of adding the fibrate component to statin treatment in order to achieve biochemical control is considered validated and applies equally to the clinical trial population and the proposed therapeutic indication. These results are supported by other published datasets that used smaller groups, as well as by large phase III clinical trials such as ACCORD- LIPID and FIELD trials. The effects on TG and HDL-C levels may be understood to reduce the residual CV risk. It is recognised that the fibrates are indicated in this manner and are used to achieve these therapeutic goals in clinical practice. An additional potential advantage of the combination therapy is one of compliance.

Uncertainty in the knowledge about the beneficial effects

Whilst an effect on TGs and HDL-C levels was established, the majority of trials failed to meet the pre-specified non-inferiority margin of 4% for LDL-C reduction. There were consistent treatment-by-gender interactions i.e., only females appeared to meet the margins in studies 0501, 0502 and 0503, which complicated the interpretation of the trials. Furthermore, a substance interaction was noted between the two components, leading to a reduction of exposure to simvastatin acid by approximately 30-40%. This substance interaction is not only relevant for the fixed dose combination but also for the free associations used in clinical practice.

The treatment by gender interaction finding remains to be fully explained, but in light of the beneficial effects on biochemical parameters in both males and females this lack of understanding is no reason for objection. Indeed the totality of evidence is reassuring such that not only will the fibrate component benefit HDL-C and TG levels, but efficacy on LDL-C will be exerted by the combination. In respect of the substance interaction, long-term data from ACCORD provide reassurance that simvastatin can exert its effect on LDL-C in the presence of fenofibrate and no difference in mean LDL-C levels were noted in the two arms possibly suggesting that interaction did not influence mean LDL-C levels. The CHMP considered that this issue is not significant in light of the clinical data, including the data from ACCORD, and the restricted indication.

Notwithstanding the fact that the proposed therapeutic indication is based on biochemical parameters alone, it is uncertain whether the combination offers any reduction of clinical events in comparison to treatment with a statin alone, since this aspect was not studied in the current development programme using the FDC. The ACCORD and FIELD trials have not demonstrated any outcome benefit in terms of overall mortality in the entire trial population but subgroup analyses suggest that in specified subset of patients, the expected benefit can be observed. The main claim from ACCORD trial, that there was a reduction of CV events in 17% of the population, is derived from post-hoc analysis. Nevertheless, in the end this is an uncertainty that impacts the decision to prescribe the medicine.

Risks

Unfavourable effects

Within the development programme, there were few new adverse events and those observed were consistent with the current level of knowledge of the mono-components. The commonest AEs were laboratory abnormalities; of which the increase in creatinine level was the most prominent. The effect of fenofibrate on creatinine is well documented and there were very few patients who progressed to acute or chronic renal failure, which is considered reassuring by the CHMP. No increase in muscle toxicity or rhabdomyolysis was reported but this may have been due to the relatively small size of the database. The frequency of AEs did not differ between the co-administration and statin monotherapy in any one study but differed between studies; lowest in 0503 (approximately 20% for each 12 week period) and highest in 0502 (approximately 33%). One hundred treatment emergent serious adverse events (TESAEs) were reported during the 24-week double blind period with an overall frequency of 3.7% in both treatment groups. For muscle effects, the standardised query showed a frequency of 2.2% in the co-administration group and 1.9% in the statin monotherapy group with only three serious events in total. Myalgia was the most commonly reported muscular AE although its frequency was below 2%. Other muscular signs/symptoms were uncommon. No cases of rhabdomyolysis were reported. There were 14 deaths in this clinical programme with 2474 patients randomised into the double blind 24-week treatment period and 1602 receiving the combination (via co-administration) in the 28-weeks open extension period. Thus, no major issues with respect to AEs could be acknowledged.

Uncertainty in the knowledge about the unfavourable effects

The primary uncertainty of the fixed dose combination relates to the effect of the interaction in the long term. While there are issues about differential efficacy, based on M13-953 study, the CHMP considered that the clinical importance of these interactions is small. The two agents have independent claims for LDL-C level reductions; fenofibrate by 15-25% by lipolytic mechanism and simvastatin by 20-35% in a dose dependent manner inhibiting the HMG Co-A reductase. If a complimentary action is anticipated, combined effect greater than the individual parts should have been evident. However, such an effect is not seen in the pivotal studies, especially for the lower dose formulation and there is still at least a theoretical risk for reducing the effect of statin even in the controlled population. Nevertheless, it appears that the magnitude of the interaction is comparable to that observed with the free association used at different times, and this is an established therapeutic practice and hence, considered clinically manageable by the CHMP.

There is a clinical evidence to suggest that statins as a class raise blood glucose in patients with high risk of diabetes. This risk, however, is outweighed by the reduction of vascular risk with statins and therefore, should not be a reason for stopping statin treatment. Given the fact that both components cause myopathy and rhabdomyolysis by different mechanisms, there is a possibility that the incidence of such effect could be increased with the fixed combination product. The homocysteine levels are known to increase with the use of fenofibrate and these are associated with an increased risk of CV events, venous thromboembolic events and possibly cognitive disorders and bone fractures. Increases in homocysteine levels have also been associated with higher levels of serum creatinine. Venous thromboembolic disease is thus appropriately listed in the RMP of Cholib.

Benefit-risk balance

Importance of favourable and unfavourable effects

The favourable effects, such as the significant reduction of triglycerides or the increase in HDL-C levels and thus, the residual risk in those patients who have an adequate response on LDL-C to simvastatin monotherapy, would be the useful additions in the high-risk population patients. The most crucial aspect of this effect is the evaluation of whether these will function as appropriate surrogates for clinical outcomes. It is currently recognised that fibrates are indicated in this manner and are used to achieve these goals in clinical practice. In relation to effects on HDL-C and TG levels, maintaining control of LDL-C is of greatest importance since the surrogacy of this parameter has been fully established. Regarding the unfavourable effects, both compounds are associated with adverse effects as expected for the combination product and no new events were identified during the current development programme.

Benefit-risk balance

Discussion on the benefit-risk balance

The combination of fenofibrate and simvastatin, at the dose strengths proposed, has a clinical rationale and indeed the medicines are used together in clinical practice. The clinical trial data confirm the expected effects of both components in terms of efficacy of lipid parameters and in terms of safety. The added benefit on TG and HDL-C for adding the fibrate component offsets the additional toxicity. There are some uncertainties in relation to a pharmacokinetic interaction between substances, but this also impacts the free association of these medicines. The published data, in particular from ACCORD, put the clinical trial data into some clinical context and offers reassurance that the substance interaction does not have important consequences on control of LDL-C levels in the longer term. Risk-benefit of Cholib is positive for the proposed indication.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of *Cholib indicated as adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase HDL - C levels when LDL - C levels are adequately controlled with the corresponding dose of simvastatin monotherapy,*
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITION

Divergent Positions

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

The reasons for divergent opinion were as follows:

Whilst the combination has a clinical rationale and whilst the fibrate component has demonstrated a beneficial effect on HDL-C and TG levels, uncertainty remains as to whether the same magnitude of effect on LDL-C will be retained by Cholib following a switch from simvastatin monotherapy. In particular:

- there is a pharmacokinetic interaction between the two substances, characterised in relatively small clinical pharmacology studies that measured only the impact on the parent compound and the major active metabolite. The mechanism for the interaction is not understood.
- there is a formulation effect with failure to show bioequivalence for the C_{max} of the parent compound for the lower dose strength.
- the clinical data presented in the dossier do not relate directly to the patient population in whom LDL-C levels are already controlled by the corresponding dose of simvastatin, and are complicated to interpret because of failure to meet the pre-specified non-inferiority margins and a magnitude of treatment effect that differs by gender.

Whilst the clinical impact of these uncertainties is potentially small, there are only marginal benefits for a fixed dose combination compared to concomitant administration; indeed, any reduced flexibility for titration may be detrimental to patient management in light of the above uncertainties.

London, 27 June 2013

…….	…….
Robert Hemmings (Co-opted member)	Alar Irs (Estonia)
…….	…….
Pierre Demolis (France)	Nevenka Trsinar (Slovenia)
…….	…….
Agnes Gyurasics (Hungary)	Ian Hudson (United Kingdom)
…….	
Nela Vilceanu (Romania)	